

Management of HIV-1 infection in adults

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Despite significant changes made over the past few years in the management of human immunodeficiency virus (HIV), infection with HIV remains a leading cause of death throughout many regions of the world. According to the Joint United Nations Programme on HIV/AIDS 2008 report on the global AIDS epidemic, 30.8 million adults and 2 million children were living with HIV at the end of 2007 (1). In 2007, 2.7 million people became infected and 2 million people died of HIV (1). In the United States, approximately 1,185,000 people are HIV infected, and 24% to 27% of patients are unaware that they are HIV-positive. Furthermore, the Centers for Disease Control and Prevention estimated that approximately 56,300 people were newly infected with HIV in 2006 (2, 3).

The development of antiretroviral therapy has dramatically altered the progression of disease caused by HIV and significantly improved the quality of life for many HIV-infected patients. Currently, 30 antiretroviral drugs are approved by the Food and Drug Administration (FDA) and available in the United States. These agents are approved for use in various combinations to prevent the emergence of resistant virus. The primary goals of antiretroviral therapy are to restore and preserve immunologic function, to reduce HIV-related morbidity, to prolong survival, and to improve quality of life. In order to optimize therapeutic outcomes and improve the patient's quality of life, a thorough understanding of the pharmacological and pharmacokinetic properties of HIV medications is essential for clinicians managing HIV-infected patients. In November 2008, the Department of Health and Human Services published its updated guidelines to provide the most current recommendations for the use of antiretroviral therapy in patients with HIV infection (4, 5).

TREATMENT INITIATION

The risks and benefits of antiretroviral therapy should be considered before initiating treatment in a patient. Additionally, the clinician should ensure that the patient has full understanding of the short-term and long-term adverse effects and the lifetime commitment with HIV treatment. Therapy is recommended for all patients with a history of AIDS-defining illness or with a CD4 T-cell count <200 cells/mm³ because they are at a higher risk for the development of opportunistic infections (Table 1). Currently, no randomized clinical trial definitively addresses the optimal time to initiate HIV treat-

Table 1. Recommendations for initiating antiretroviral therapy in treatment-naïve adults with established HIV-1 infection

Clinical condition	CD4 cell count (cells/mm ³)	Recommendations
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Initiate antiretroviral therapy.
Asymptomatic	<350	Initiate antiretroviral therapy.
Asymptomatic	≥ 350	Individualize therapy; the optimal time to initiate therapy in asymptomatic patients is not well defined.

ment in patients with a CD4 T-cell count between 200 and 350 cells/mm³. The guidelines support the use of antiretroviral therapy in all individuals with a CD4 T-cell count <350 cells/mm³ based on several long-term, observational, cohort studies. In special populations such as pregnant women, patients with HIV-associated nephropathy, patients with HIV coinfecting with hepatitis B when treatment is indicated, and symptomatic patients, treatment should be initiated regardless of CD4 T-cell count in order to maximize viral suppression, prevent HIV transmission, and prolong survival (4–7).

INITIAL TREATMENT OPTIONS

Due to the increasing resistance of HIV to single-drug therapy, a combination of antiretroviral drugs known as highly active antiretroviral therapy (HAART) is preferred as initial treatment. Studies have shown that HAART is highly effective in suppressing HIV replication and improving survival among HIV-infected patients (6). The current guidelines recommend that HAART should contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI) with or

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Table 2. Characteristics of antiretroviral agents

Nucleoside reverse transcriptase inhibitors			
Mechanism of action	Interferes with HIV RNA-dependent DNA polymerase, resulting in chain termination and inhibition of viral replication		
Class adverse effects	Lactic acidosis with hepatic steatosis		
Drug name	Dose		Adverse effects
Abacavir (Ziagen or ABC)	300 mg BID		Hypersensitivity reaction with symptoms that may include fever, rash, nausea, vomiting, malaise or fatigue, respiratory difficulties; do not rechallenge, test for HLAB*5701
Didanosine (Videx EC or ddl)		<60 kg	≥60 kg
	EC capsule	250 mg daily	400 mg daily
	With tenofovir	200 mg daily	250 mg daily
Emtricitabine (Emtriva or FTC)	200 mg daily or 240 mg (24 mL) solution daily		Headaches, fatigue, nausea, pigmentation of palms/soles
Lamivudine (EpiVir or 3TC)	150 mg BID or 300 mg daily		Headaches, fatigue, nausea; generally well tolerated
Stavudine (Zerit or d4T)	<60 kg	≥60 kg	
	30 mg BID	40 mg BID	
Tenofovir (Viread or TDF) mono-phosphorylated NRTI	300 mg daily		Decreased phosphate, nausea, upset stomach; rare: renal insufficiency, Fanconi syndrome
Zidovudine (Retrovir or AZT)	300 mg BID or 200 mg TID		Headache, nausea, increased pigmentation of skin/nails, neutropenia, anemia, myopathy
Non-nucleoside reverse transcriptase inhibitors			
Mechanism of action	Direct nonnucleoside inhibitors of HIV-1 reverse transcriptase, interacting at allosteric site		
Class adverse effects	Hepatotoxicity, rash, SJS (which may accompany hepatic failure in about half of patients)		
Drug name	Dose		Adverse effects
Delavirdine (Rescriptor or DLV)	400 mg TID		Headache, rare neutropenia/anemia, hepatotoxicity
Efavirenz (Sustiva or EFV)	600 mg daily at bedtime		Rash, altered liver function, dizziness, insomnia, impaired concentration, drowsiness, abnormal dreams; contraindicated in pregnancy, particularly in the first trimester
Etravirine (Intelence)	200 mg BID		Rash, nausea, elevated liver enzymes, peripheral neuropathy; rare: SJS, myocardial infarction, hypersensitivity reaction
Nevirapine (Viramune or NVP)	200 mg daily x 14 days, then 200 mg BID or 400 mg daily		Rash (usually occurs within first 6 weeks; drug should be discontinued if severe), severe hepatotoxicity, SJS/toxic epidermal necrolysis; should not be initiated in women with CD4 >250 cells/μL or men with CD4 >400 cells/μL
Protease inhibitors			
Mechanism of action	Inhibits cleavage of polyproteins that are required for formation/maturation of infectious virions at the end of the HIV life cycle (i.e., budding)		
Class adverse effects	Hyperlipidemia (except atazanavir), hyperglycemia, increased transaminases, increased bleeding in hemophiliacs		
Drug name	Dose		Adverse effects
Atazanavir (Reyataz or ATV)	Treatment naive: 400 mg daily Treatment exposed: 300 mg plus RTV 100 mg daily		Increased unconjugated bilirubinemia, nephrolithiasis, may prolong PR interval, low risk of lipid abnormalities
Darunavir (Prezista or TMC114)	600 mg plus RTV 100 mg BID		Rash, abdominal pain, constipation, headache, hepatotoxicity, caution with sulfa allergy
Fosamprenavir (Lexiva or LXV)	1400 mg BID or Treatment naive: 1400 mg plus RTV 100 to 200 mg daily; treatment exposed: 700 mg plus RTV 100 mg BID		Diarrhea, nausea, rash, caution with sulfa allergy
Indinavir (Crixivan or IDV)	800 mg plus RTV 100 to 200 mg BID		Nephrolithiasis, increased unconjugated bilirubinemia, metallic taste, jaundice or hepatitis
Lopinavir/ritonavir (Kaletra or LPV/r)	Treatment naive: 4 tablets daily Treatment exposed: 2 tablets BID		Taste alterations, diarrhea, nausea (increased with daily dosing), fatigue, asthenia
Nelfinavir (Viracept or NFV)	1250 mg BID 750 mg TID		Diarrhea (treat with calcium carbonate 500 mg BID, Metamucil BID, or loperamide), nausea
Ritonavir (Norvir or RTV)	100 to 200 mg with PIs		GI intolerance, asthenia, taste disturbances, paresthesias, pancreatitis, metabolic abnormalities
Saquinavir (Invirase or SQV)	1000 mg plus RTV 100 mg BID		GI intolerance, headache
Tipranavir (Aptivus or TPV)	500 mg plus RTV 200 mg BID		Caution with sulfa allergy, hepatotoxicity (some fatal cases), fatal/nonfatal intracranial hemorrhage, nausea, diarrhea, vomiting

Adapted from Department of Health and Human Services guidelines (6).

BID indicates twice daily; TID, three times a day; GI, gastrointestinal; SJS, Stevens-Johnson syndrome.

Table 3. Antiretroviral components recommended for treatment of HIV-1 infection in treatment-naive patients

	Option 1: NNRTI plus choice of PI		Option 2
	NNRTI	PI	Dual NRTI
Preferred	Efavirenz	Atazanavir + ritonavir Darunavir + ritonavir Fosamprenavir + ritonavir Kaletra	Tenofovir/emtricitabine (Truvada)
Alternative	Nevirapine	Atazanavir (unboosted) Fosamprenavir (unboosted) Fosamprenavir + ritonavir Saquinavir + ritonavir	Abacavir + lamivudine OR Zidovudine/lamivudine (second line) OR Didanosine + (emtricitabine or lamivudine) (third line)

NNRTI indicates non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitors.

without ritonavir boosting. However, it is important to further individualize therapy based on virologic efficacy, compliance, comorbid conditions, and potential drug-drug interactions (*Tables 2 and 3*). Currently six antiretroviral classes are FDA approved for the treatment of HIV-1 infection. These include the NRTIs, NNRTIs, PIs, fusion inhibitors, chemokine coreceptor 5 (CCR5) antagonists, and integrase inhibitors (4–6).

NRTIs

NRTIs exert their antiretroviral effect by interfering with HIV RNA-dependent DNA polymerase, resulting in chain termination and inhibition of viral replication. The medications in this class are not metabolized by the cytochrome P450 isoenzyme and do not pose concerns with regard to drug interactions with medications metabolized by this system (6, 8). Dosage adjustment is necessary in renal insufficiency because most NRTIs are renally eliminated. Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity that is associated with NRTIs. Some adverse effects reported with the use of NRTIs include gastrointestinal intolerance, anorexia, generalized weakness, weight loss, and hepatomegaly. The selection of drugs should be based on their efficacy, adverse effect profile, and potential additive toxicities. Therefore, concomitant use of didanosine and stavudine should be avoided because of an additive risk for pancreatitis and peripheral neuropathy (6, 7). The typical dual-NRTI combinations used in clinical practice consist of an NRTI in combination with lamivudine or emtricitabine because these agents have fewer side effects (5, 6, 9).

The combination of tenofovir with emtricitabine (Truvada) or lamivudine in combination with several different boosted PIs demonstrated good virologic benefit in several randomized clinical trials. The use of tenofovir with either lamivudine or emtricitabine as part of an efavirenz-based regimen in treatment-naive patients demonstrated potent virologic suppression and was superior to zidovudine/lamivudine in virologic efficacy at up to 144 weeks (6, 12). Tenofovir is generally well tolerated, and its adverse effects are mostly

associated with headache and gastrointestinal intolerance such as nausea, diarrhea, and vomiting. Cases of renal impairment, hypophosphatemia, and Fanconi syndrome have been reported with tenofovir. Truvada is currently the preferred NRTI combination for naive patients with creatinine clearance >30 mL/min (6, 13, 14).

Another dual-NRTI combination that is commonly used as part of HAART is abacavir with lamivudine (Epzicom). The use of abacavir plus lamivudine demonstrated a significant viral suppression in a comparative trial with zidovudine plus lamivudine (10). Subjects from both arms achieved similar virologic responses; however, abacavir-treated subjects experienced a greater CD4 cell increase at 48 weeks. One disadvantage with the use of abacavir is its potential for hypersensitivity reactions. Approximately 5% to 8% of patients receiving abacavir have developed a potentially life-threatening hypersensitivity reaction.

Patients should undergo HLAB*5701 testing prior to treatment with abacavir. Epzicom is recommended as an alternative dual-NRTI combination for patients who have tested negative for HLAB*5701 (6, 11). (See Table 4 for a list of one-tablet combination pills.)

NNRTIs

Another HIV class that is recommended as part of HAART for the initial therapy in antiretroviral-naive patients is the NNRTIs. The antiretroviral effect of NNRTIs is mediated through the inhibition of reverse transcriptase. NNRTIs block the RNA-dependent DNA polymerase activities including HIV-1 replication. Additionally, NNRTIs do not require intracellular activation for antiviral activity (7, 15). The class is mainly metabolized by the liver, but each NNRTI has different effects on the cytochrome P450 enzymes. For example, nevirapine is an inducer of cytochrome 3A4, and delavirdine is a cytochrome 3A4 inhibitor; efavirenz and etravirine have mixed effects. Therefore, drug interactions with other medications that are metabolized by cytochrome P450 must be carefully monitored, and dose adjustments must be made accordingly (5, 9, 16). As a class, the NNRTIs are generally associated with rare but severe and life-threatening cases of Stevens-Johnson syndrome and toxic epidermal necrolysis (6, 7, 15).

One of the preferred combinations for initial HIV treatment is an NNRTI plus two NRTIs. The NNRTI-based regimen is effective and has fewer chronic side effects compared with the PI-based regimen. A significant limitation with the use of NNRTI regimens is that a single mutation in the reverse transcriptase can produce a virus resistant to all NNRTIs and lead to virologic failure in 7% of patients (6, 15, 17). However, NNRTIs usually consist of fewer pills and are better tolerated, which can improve adherence and tolerability for patients. The two NNRTIs that are currently being recommended as a component of HAART are efavirenz and nevirapine (4, 18).

The AIDS Clinical Trials Group study A5142 found that efavirenz plus two NRTIs resulted in a longer time to virologic

Table 4. Single-tablet regimens

Brand name	Composition	Dose
Epzicom	Abacavir 600 mg, lamivudine 300 mg	1 tablet daily
Trizivir	Abacavir 300 mg, zidovudine 300 mg, lamivudine 150 mg	1 tablet twice daily
Combivir	Zidovudine 300 mg, lamivudine 150 mg	1 tablet twice daily
Truvada	Tenofovir 300 mg, emtricitabine 200 mg	1 tablet daily

failure and lower rate of virologic failure compared with lopinavir/ritonavir (Kaletra) plus two NRTIs (6, 16). Efavirenz is generally well tolerated and available in a single pill coformulated with tenofovir plus emtricitabine that is given once daily. A major disadvantage of efavirenz is its central nervous system side effects that include vivid dreams, hyperexcitability, nightmares, and hallucinations, which usually resolve after a few weeks. Other rare but serious adverse effects include rash, elevated liver enzymes, and potential teratogenic effects. On the other hand, efavirenz is rarely associated with major serum lipid abnormalities and alterations in body fat distribution. Efavirenz, therefore, is one of the preferred NNRTI-based regimens (6, 9).

A second NNRTI that can be used as an alternative to efavirenz for initial treatment of antiretroviral-naive patients is nevirapine. A randomized open-label study comparing nevirapine with efavirenz in combination with lamivudine and stavudine found that nevirapine had a rate of virologic suppression comparable to that of efavirenz (19). Nevirapine is also relatively well tolerated and less likely to cause serum lipid abnormalities. Hepatic failure and potentially life-threatening skin reactions including rash have been reported with nevirapine during the first 18 weeks of therapy (6, 20). Additionally, nevirapine should be avoided in women with CD4 counts >250 cells/mm³ and men with CD4 counts >400 cells/mm³ due to an increased risk of hepatitis. Overall, nevirapine can be used as an alternative NNRTI-based regimen for patients who cannot tolerate efavirenz (6, 7, 15).

PIs

A PI is another preferred agent that can be used as a backbone for HAART. The antiretroviral effects of PIs are mediated through the inhibition of the protease enzyme. PIs block the HIV-1 protease, thereby preventing the cleavage of the gag-pol polyproteins and subsequently inducing the formation of immature, noninfectious virus (6, 18). In general, PIs have many potential drug interactions since they are metabolized by the cytochrome 3A4 enzyme. Monitoring for drug-drug interactions is essential in order to reduce toxicities and loss of therapeutic effectiveness (6, 8). Some common adverse effects associated with PIs are nausea, vomiting, diarrhea, hyperglycemia, elevated liver enzymes, increased risk of bleeding in hemophiliacs, lipid abnormalities, and alterations in body fat distribution. PI-containing regimens can be difficult to adhere to because of the dosing frequency, food restrictions, and side effects. However, PIs are potent antiretroviral drugs, and they have been shown

to be effective in durably reducing viral load in antiretroviral-naive patients (6, 7).

The combination of ritonavir-boosted atazanavir plus two NRTIs has been shown to be effective in suppressing viral replication and is recommended as one of the initial regimens. Atazanavir offers an advantage of once-daily dosing and has fewer adverse effects on lipid metabolism than other PIs. A study found that atazanavir and nelfinavir have comparable efficacy, but atazanavir is less likely to cause diarrhea (16). The most frequent adverse effect associated with atazanavir is indirect hyperbilirubinemia that sometimes can lead to jaundice or sclera icterus. Additionally, severe cases of nephrolithiasis and asymptomatic first-degree atrioventricular block have been reported (6, 21, 22).

Ritonavir-boosted darunavir is another preferred PI for treatment-naive patients. In antiretroviral-naive patients, darunavir plus ritonavir was compared with lopinavir/ritonavir; both groups were given tenofovir/emtricitabine. At 48 weeks, darunavir/ritonavir was demonstrated to be noninferior to lopinavir/ritonavir in the rates of viral suppression. The most common symptomatic adverse effects associated with darunavir include diarrhea, nausea, headache, and rash. Liver toxicity, including severe hepatitis, has been reported with darunavir, especially in patients with chronic hepatitis B or C or other chronic liver disease. Severe skin rash, including erythema multiforme, and Steven-Johnson syndrome were reported during the development program of darunavir. Additionally, darunavir should be used cautiously in patients with sulfonamide allergy since it contains a sulfonamide component (6, 15).

Another preferred PI-based regimen is ritonavir-boosted fosamprenavir plus two NRTIs. Fosamprenavir is a prodrug of amprenavir that can be dosed twice daily. Like ritonavir-boosted atazanavir and Kaletra, resistance to ritonavir-boosted fosamprenavir is uncommon in HIV-naive patients. Metabolic toxicity, including dyslipidemia and insulin resistance, has been reported with fosamprenavir. Overall, fosamprenavir is generally well tolerated, but it should be used with caution in patients with sulfa allergies since it has a potential cross-sensitivity with sulfonamides (6, 23).

Kaletra is an alternative PI-based regimen for treatment-naive patients. A randomized study comparing ritonavir-boosted fosamprenavir with Kaletra found that they have comparable virologic responses at 96 weeks. Furthermore, several clinical trials have shown that Kaletra with two NRTIs has sustained antiretroviral activity with minimal development of viral resistance mutations (16, 20). A major drawback with Kaletra is that its adverse effects include gastrointestinal intolerance (e.g., diarrhea), hyperglycemia, and hyperlipidemia (e.g., hypertriglyceridemia). On the other hand, Kaletra-based regimens have potent virologic activity and less drug resistance associated with virologic failure (6, 23).

Fusion inhibitor

Unlike other HIV agents, enfuvirtide (Fuzeon) is a fusion inhibitor that binds to the gp41 protein of the virus and prevents the virus from infecting healthy cells. Due to its

fragile structure, enfuvirtide must be given in an injectable form. The recommended dose for enfuvirtide is 90 mg given subcutaneously twice daily. Since enfuvirtide is catabolized by proteolytic enzymes, there are no known clinically significant interactions between enfuvirtide and other medications. The most common adverse effect associated with enfuvirtide is injection-site reaction. Other adverse effects that have been reported with enfuvirtide include rash, fever, peripheral neuropathy, insomnia, depression, decreased blood pressure, increased bacterial pneumonia, and elevated liver enzymes. Currently, treatment guidelines do not recommend enfuvirtide as initial therapy since there is no clinical trial experience in treatment-naïve patients. Thus, enfuvirtide is likely to be reserved for salvage therapy (6, 24).

Recently approved treatments

Recently approved drugs can be used against resistant strains, whose prevalence is increasing. The CCR5 antagonist and integrase inhibitors are two new drug classes, and etravirine is a new NNRTI agent recently approved by the FDA for the treatment of HIV-1 infection in treatment-experienced patients. Due to the limited clinical trial data available, they are not recommended as part of the initial regimen. The pharmacokinetic parameters of these new agents have not been established in pediatric or pregnant patients. The three new drugs in these classes are etravirine, maraviroc, and raltegravir (6).

Etravirine is a new NNRTI agent that was approved by the FDA in January 2008 to be used in combination with other anti-HIV medications for treatment-resistant patients. Etravirine is a cytochrome 3A4 inhibitor as well as a 2C9 and 2C19 inducer; therefore, it has therapeutically significant interactions with many medications. Dose adjustment may be necessary depending on the potential drug-drug interactions. The most common adverse events reported with etravirine are rash, nausea, and elevated liver enzymes. Rare cases of Stevens-Johnson syndrome, myocardial infarction, and hypersensitivity reactions have been reported with the use of etravirine (6, 25, 26).

Maraviroc is an antiretroviral agent for the treatment of CCR5-tropic HIV. It is the first in a new class of antiretrovirals that block HIV entry into human cells by its predominant entry route, the CCR5 coreceptor. Maraviroc is effective at reducing viral load only in patients with the CCR5-tropic HIV strain; CCR5 tropism testing should be done prior to initiating maraviroc. Maraviroc should be used in combination with other antiretroviral agents. The recommended starting dose of maraviroc is 300 mg twice daily in adults. It is a 3A4 substrate; therefore, the dosage of maraviroc should be adjusted if it is taken with a strong cytochrome 3A4 inhibitor or inducer. Some adverse effects of maraviroc include cough, upper respiratory tract infection, muscle and joint pain, and sleep disturbance. Myocardial ischemia and hepatitis have been observed in patients receiving maraviroc (6, 27).

Raltegravir is the first agent in the class of integrase inhibitors. It prevents viral replication by inhibiting viral DNA insertion into the host cell genome. The recommended dose of raltegravir is 400 mg given orally twice daily. Raltegravir does not interact with the hepatic cytochrome 450 enzyme; it is

metabolized mainly by glucuronidation. Creatine phosphokinase increases have been observed, and myopathies and rhabdomyolysis have been reported. Therefore, raltegravir should be used with caution in patients already at risk for creatine phosphokinase elevations. The most common adverse events reported with raltegravir are diarrhea, nausea, headache, and abnormal dreams (6, 28).

ANTIRETROVIRAL THERAPY IN SPECIAL POPULATIONS

Pregnant women

Prevention and treatment of HIV disease in pregnant women have evolved significantly in the United States over the last decade. The transmission rate from the mother to infant is approximately 20% to 30% (29). In 1994, the Pediatric AIDS Clinical Trial Group protocol 076 demonstrated that zidovudine-based regimens given during pregnancy and labor and to the neonate after delivery significantly reduced perinatal HIV transmission (30). The 2008 US Public Health Service-issued guidelines recommended the use of combination drug regimens for the treatment of HIV infection and prevention of perinatal HIV transmission. The current strategy to prevent perinatal HIV transmission is use of zidovudine-based combination regimens. The guidelines recommend that antiretroviral prophylaxis should be offered to all HIV-infected pregnant women regardless of CD4 cell count to prevent perinatal HIV transmission. Due to limited data on the use of HIV agents in pregnant women and effects on the developing fetus, long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy (6, 29, 31–33).

Coinfection with hepatitis viruses and HIV

Patients coinfecting with HIV and liver disease such as hepatitis B (HBV) or hepatitis C (HCV) have experienced a more rapid progression of liver disease compared with patients infected with HBV or HCV alone. Initiation of antiretroviral therapy should be considered at any CD4 cell count in HIV patients coinfecting with HCV to reduce the rate of progression of liver disease. Patients with adequately controlled HIV disease (CD4 cell count >200 cells/mm³) and chronic hepatitis C on liver biopsy should be evaluated for HCV treatment. For patients with lower CD4 counts, HCV therapy should be delayed since concurrent treatment can be complicated by drug toxicities, adherence, and limited efficacy. In HBV coinfection, treatment should be initiated regardless of CD4 cell count. Treatment of HBV with emtricitabine, lamivudine, and tenofovir is appropriate since they have activity against both HIV and HBV. Unfortunately, treatment of HIV with antiretroviral therapy may result in severe hepatotoxicity in coinfecting patients; therefore, antiretroviral therapy should be administered cautiously and liver function tests performed (5, 6).

CONCLUSION

New advances in the management of HIV infection and recent data on treatment selection have dramatically altered the natural progression of infection and significantly improved the

quality of life for many HIV-infected patients. As a result, there has been a pronounced decline in the reported number of new AIDS-related opportunistic infections and deaths. Despite these remarkable advances, disease management remains challenging because of long-term toxicities, adverse events, HAART failures, and the HIV infection itself. These problems continue to limit the effectiveness of HAART and present major challenges in managing HIV infection. By understanding the principle of HIV therapy, the clinician can individualize antiretroviral therapy for the patient by minimizing adverse events and improving patient compliance and clinical outcomes.

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