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Antiretroviral Therapy: a Primer for Dermatologists

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Combination antiretroviral therapy (ART) has transformed the care of individuals with HIV infection. Effective ART has resulted in dramatic reductions in mortality, hospitalization rates, and the development of AIDS-defining illnesses [1,2].

Currently the Food and Drug Administration has approved 21 antiretroviral drugs, and additional agents are in testing. Despite the considerable benefits of ART, the medications do present a set of management issues including major adverse effects, drug interactions, drug resistance, and the consequences of poor adherence.

This article discusses the variety of agents that can comprise an effective ART regimen, focusing on the basic principles of ART, the indications for initiating ART in treatment-naive individuals who have established HIV infection, and the challenges associated with the use of antiretroviral medications.

Principles of antiretroviral therapy and when it should be initiated

The goal of ART is to obtain maximal and durable suppression of HIV, restore and preserve immune function, improve quality of life, and reduce HIV-related morbidity and mortality. Before starting ART, the clinician must give careful consideration to the patient's social and medical condition. In general, the patient should be both interested in and able to take antiretroviral medications consistently. Active personal and social problems (eg, ongoing drug use, homelessness, or unstable psychiatric conditions) can be major obstacles to successful ART and should be addressed before initiating ART. In addition, ART should be deferred until any active significant medical problems are stabilized. The decision to start ART is based on the patient's clinical status, CD4 T-cell count, and plasma HIV RNA level. There are many possible antiretroviral drug combinations, but some are considered preferred regimens based on published studies demonstrating their effectiveness and tolerability. When choosing a particular regimen, the clinician should take into account the clinical data supporting that regimen as well as the dosing schedule, pill burden, possible adverse effects or drug interactions, and underlying patient preferences.

Treatment guidelines established by the World Health Organization, by the US Department of Health and Human Resources (DHHS), and by the Henry J. Kaiser Family Foundation recommend that ART be offered to chronically infected patients who have significant HIV-related symptoms or AIDS or who are asymptomatic but meet certain immunologic or virologic thresholds [3–5].

All treatment guidelines recommend that patients who have symptomatic AIDS as well as asymptomatic patients who have CD4 T-cell counts below 200/μL be offered therapy because of the significant risk of opportunistic infection and death without treatment. Although asymptomatic patients who have CD4 T-cell counts between 200 and 350/μL can be offered treatment, the optimal time of initiation remains unclear [3,6]. Treatment generally is not recommended for asymptomatic patients who have CD4 T-cell

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counts above 350/μL, although some clinicians may consider treatment if plasma HIV RNA levels are above 100,000 copies/mL; observational data demonstrate faster rates of disease progression in this cohort [7], but these data are controversial [3].

Antiretroviral agents and choice of initial regimen

There are currently four classes of antiretroviral medications, comprising a total of 21 drugs (Table 1):

1. Nucleoside reverse transcriptase inhibitors (NRTIs): abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate (tenofovir-DF), zalcitabine, and zidovudine
2. Nonnucleoside reverse transcriptase inhibitors (NNRTIs): delavirdine, efavirenz, and nevirapine
3. Protease inhibitors: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir plus ritonavir, nelfinavir, ritonavir, and saquinavir
4. Fusion inhibitors: enfuvirtide

ART should consist of a regimen that includes a combination of three or more medications. Initial regimens typically consist of a backbone of two NRTIs, plus an NNRTI, a protease inhibitor, or a boosted protease inhibitor. In a boosted protease inhibitor, small doses of

Table 1
Antiretroviral medications

Generic name	Trade name	Dosage[a]
Nucleoside RTIs		
Abacavir (ABC)	Ziagen	300 mg bid
Didanosine (ddI)	Videx	400 mg qd (250 mg qd if < 60 kg)
Emtricitabine (FTC)	Emtriva	200 mg qd
Lamivudine (3TC)	Epivir	150 mg bid
Stavudine (d4T)	Zerit	40 mg bid (30 mg bid if < 60 kg)
Zalcitabine (ddC)	Hivid	0.75 mg tid
Zidovudine (AZT)	Retrovir	300 mg bid or 200 mg bid
Zidovudine + lamivudine	Combivir	One tablet bid
Zidovudine + lamivudine + abacavir	Trizivir	One tablet bid
Nucleotide RTIs		
Tenofovir	Viread	300 mg qd
Emtricitabine + tenofovir	Truvada	200/300 mg qd
Nonnucleoside RTIs		
Delavirdine	Rescriptor	400 mg tid
Efavirenz	Sustiva	600 mg qd (dose can be split and given 200 mg in AM and 400 mg in PM)
Nevirapine	Viramune	200 mg qd × 14 days, then 200 mg bid
Protease inhibitors		
Atazanavir (ATV)	Reyataz	400 mg qd or (ATV 300 mg + RTV 100 mg qd)
Darunavir (DRV)[b]	Prezista	DRV 600 mg + RTV 100 mg bid
Fosamprenavir (f-APV)	Lexiva	Treatment-naive patients: 1400 mg bid or (f-APV 1400 mg + RTV, 200 mg qd) or (f-APV 700 mg + RTV, 100 mg bid)
Indinavir (IDV)	Crixivan	800 mg q 8 hr or (IDV 800 mg + RTV 100 or 200 mg bid)
Lopinavir + ritonavir (LPV/r)	Kaletra	LPV 400 mg bid + RTV 100 mg bid
Nelfinavir (NFV)	Viracept	1250 mg bid or 750 mg tid
Ritonavir (RTV)	Norvir	600 mg bid or as a pharmacologic booster: 100–400 mg in 1–2 divided doses
Saquinavir (SQV)[b]	Fortovase	SQV 1000 mg + RTV 100 mg bid
Tipranavir (TPV)[b]	Aptivus	TPV 500 mg + RTV 200 mg bid
Fusion inhibitor		
Enfuvirtide (T20)	Fuzeon	90 mg SQ bid

Abbreviation: RTIs, reverse transcription inhibitors.
[a] All medications administered orally unless otherwise indicated.
[b] Unboosted dosing (without RTV) is not recommended.

ritonavir are used to increase the plasma level of a second protease inhibitor (see later discussion). Preferred regimens for antiretroviral-naive patients have been identified in the DHHS guidelines (Table 2). In contrast, for resource-limited settings, World Health Organization guidelines recommend a simpler first-line regimen of a dual NRTI of zidovudine or stavudine with lamivudine in conjunction with a NNRTI [4].

Fig. 1 shows the various stages of the HIV life cycle and the site of action of the different classes of antiretroviral agents.

The NRTIs work by incorporation into the elongating strand of viral DNA during reverse

Table 2
US Department of Health and Human Safety recommendations for antiretroviral regimens for the treatment of established HIV in antiretroviral-naive patients

		# Pills/d
NNRTI-based regimens		
Preferred	Efavirenz[a] + (lamivudine or emtricitabine) + zidovudine or tenofovir DF	2–3
Alternatives	Efavirenz[a] + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine)	2–4
	Nevirapine[b] + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir)	3–6
PI-based regimens		
Preferred	Lopinavir/ritonavir (coformulated as Kaletra) + (lamivudine or emtricitabine) + zidovudine	6–7
Alternatives	Atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir + ritonavir, 100 mg/d)	3–6
	Fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	5–8
	Fosamprenavir/ritonavir[c] + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	5–8
	Indinavir/ritonavir[c] + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	7–12
	Lopinavir/ritonavir (coformulated as Kaletra) + (lamuvidine or emitricitabine) + (stavudine or abacavir or tenofovir or didanosine)	5–8
	Nelfinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	5–8
	Saquinavir (soft gel capsule, hard gel capsule, or tablets)/ritonavir[c] + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)	7–15
Triple NRTI-based regimen[d]		
	Abacavir + zidovudine + lamuvudine	2

Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Efavirenz is not recommended for use in 1st trimester of pregnancy or in women with high pregnancy potential (ie, women who want to conceive or who are not using effective contraception).

[b] High incidence (11%) of symptomatic hepatic events was observed in women with pre-nevirapine CD4 T cell counts > 250 cells/mm^3 and men with CD4 T cell counts > 400 cells/mm^3 (6.3%). Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk.

[c] Low-dose (100–400 mg) ritonavir.

[d] Use only when a preferred or an alternative NNRTI- or PI-based regimen cannot or should not be used.

From Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. In: Recommendations of the Panel on Clinical Practices for Treatment of HIV. Bethesda (MD): US Department of Health and Human Services; 2006.

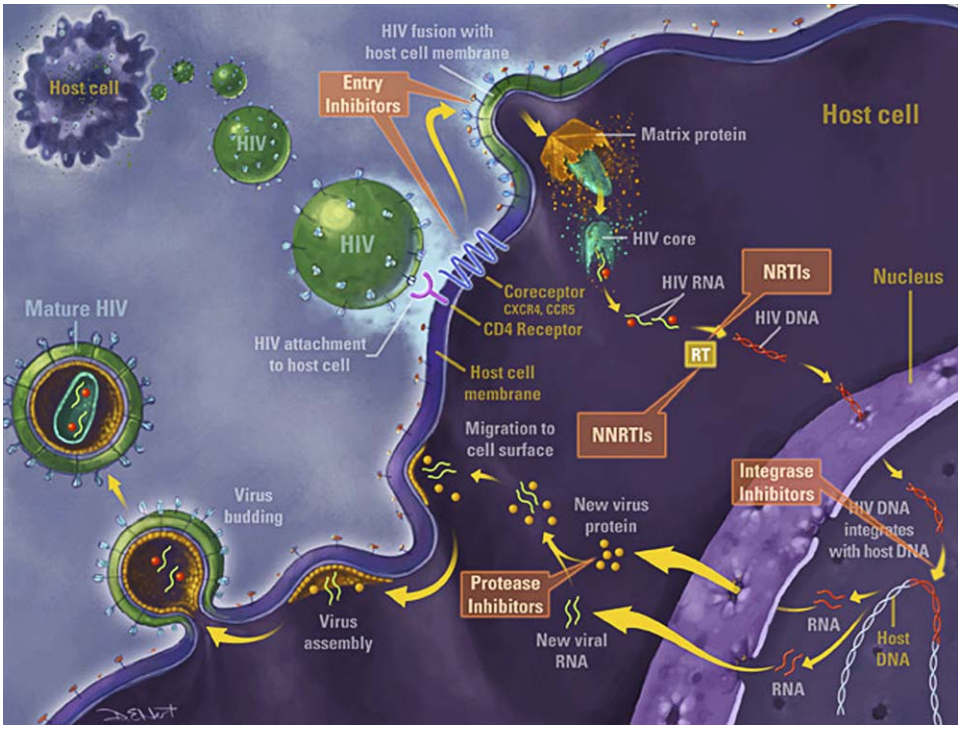

Fig. 1. Site of action of the major classes of antiretroviral agents. NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase.

transcription, causing chain termination. Agents in this class often serve as the backbone of a combination ART regimen and are less likely to cause drug interactions. They can have a variety of agent-specific adverse effects as well as class-specific toxicities including mitochondrial toxicity and lipodystrophy (Table 3).

The NNRTIs also block reverse transcriptase but do so by binding directly to reverse transcriptase in the catalytic site. Agents in this class have fewer long-term toxicities and longer half-lives resulting in more convenient dosing. Resistance to NNRTIs can occur quickly, however, with a single point mutation rendering the entire class nonfunctional—a feature that should be considered in patients who are anticipated to have difficulty with adherence.

The HIV protease inhibitors bind selectively to HIV protease and prevent this enzyme from performing its normal function of cleaving viral polyprotein precursors into individual functional proteins. Inhibition of HIV protease leads to the formation of deformed HIV particles that do not replicate. Historically, protease inhibitors carried a high pill burden and dosing frequency, significant gastrointestinal toxicity, and certain food restrictions. Newer drugs and newer formulations of older drugs have mitigated many of these problems. Protease inhibitors still are associated with long-term metabolic complications such as diabetes, insulin resistance, and fat redistribution, but, in contrast to NNRTIs, have a high threshold to drug resistance, making a protease inhibitor–anchored regimen more forgiving of lapses in adherence.

The fusion inhibitor enfuvirtide represents the newest class of antiretroviral agents. It has been studied primarily in highly treatment-experienced patients and therefore is not recommended for first-line ART. It works by binding to the gp41 envelope protein of HIV to prevent it from mediating fusion of the viral and cell membranes. Enfuvirtide is most effective in patients who have CD4 T-cell counts above 100 cells/μL; in these cases, enfuvirtide is combined with a standard regimen of drugs that includes one or two agents to which the patient's virus is sensitive. Several clinical trials have shown the highly treatment experienced patients who received an optimized background of boosted active protease inhibitor

Table 3
Adverse effects associated with antiretroviral medications

Generic name	Toxicity
Nucleoside RTIs	All nucleoside RTIs may be associated with mitochondrial toxicity, lactic acidemia, and lipodystrophy (atrophy)
Abacavir (ABC)	Hypersensitivity reaction in 3% of patients; characterized by fever, rash, nausea, vomiting, or malaise; may be fatal; lactic acidosis (rare)
Didanosine (ddI)	Peripheral neuropathy, pancreatitis, nausea, lactic acidosis, lipoatrophy
Emtricitabine (FTC	Few side effects; lactic acidosis (rare)
Lamivudine (3TC)	Few side effects; lactic acidosis (rare)
Stavudine (d4T)	Peripheral neuropathy; lactic acidosis (rare)
Zalcitabine (ddC)	Peripheral neuropathy, stomatitis, lactic acidosis (rare)
Zidovudine (AZT)	Anemia, neutropenia, gastrointestinal problems, headache, lactic acidosis (rare), lipoatrophy
Nucleotide RTIs	
Tenofovir	Renal dysfunction (unusual)
Nonnucleoside RTIs	
Delavirdine	Rash (4%); increased aminotransferase levels; headache
Efavirenz	Rash (2%); central nervous system side effects (eg, confusion, abnormal dreams, agitation)
Nevirapine	Rash (7%); increased aminotransferase levels; hepatitis (can be fatal)
Protease inhibitors	Most protease inhibitors are associated with lipid abnormalities, lipodystrophy (central fat accumulation) and gastrointestinal side effects
Atazanavir	Gastrointestinal intolerance; elevated bilirubin levels
Darunavir	Gastrointestinal intolerance; headache; nasophuryngitis
Fosamprenavir	Gastrointestinal intolerance; lipid abnormalities; perioral paresthesias; fat redistribution
Indinavir	Gastrointestinal intolerance; nephrolithiasis; increase of indirect bilirubin; headache; lipid abnormalities; fat redistribution
Lopinavir + ritonavir	Gastrointestinal intolerance; lipid abnormalities, including increased triglyceride levels; fat redistribution
Nelfinavir	Diarrhea; lipid abnormalities; major drug–drug interactions; fat redistribution
Ritonavir	Gastrointestinal intolerance; perioral and extremity paresthesias; taste perversions; asthenia; hepatitis; major drug–drug interactions; lipid abnormalities including increased triglyceride levels; fat redistribution
Saquinavir	Gastrointestinal intolerance; headache; lipid abnormalities; fat redistribution
Tipranavir	Rash (8%–14%, particularly in woman); clinical hepatitis and hepatic decompensation including some fatalities

Abbreviation: RTI, reverse transcriptase inhibitor.

with enfuviritide demonstrated higher rates of virologic suppression compared with those who received active protease inhibitors alone [8]. Patients who do not meet these criteria still may experience a virologic response and some immunologic benefit from enfuvirtide, however. These benefits must be weighed against the cost, difficulty of administration (twice-daily subcutaneous injections), and adverse effects (eg, injection-site reactions, hypersensitivity, and possible pneumonia) [9].

Integration of the viral DNA into a host cell genome is an essential step for HIV replication and maintenance of persistent infection. A number of compounds currently under investigation inhibit HIV-1 integrase, the enzyme necessary to accomplish this function (see Fig. 1).

Dosing schedules and restrictions

Practical considerations have led to the increasing use of antiretroviral regimens that have less frequent dosing schedules, minimal meal restrictions, and the fewest adverse effects. Most of the NRTIs can be taken once or twice daily without regard to food consumption; the exceptions are the little-used zalcitabine, which is taken three times per day, and didanosine, which is taken half an hour before a meal or 1 hour after a meal. The NNRTIs also are dosed daily or twice

daily and can be taken without regard to food, with the caveat that efavirenz should not be taken after a meal high in fats. Historically, dosing schedules and food restrictions were more complicated with the protease inhibitors, but newer drugs and the practice of ritonavir boosting have led to more favorable dosing profiles. Among the protease inhibitors, atazanavir, nelfinavir, saquinavir, and ritonavir should be taken with food; fosamprenavir can be taken with or without meals; unboosted indinavir should be taken 1 hour before or 2 hours after a meal or can be taken with a low-fat meal.

Combination therapy

Increasingly, pharmacologic boosting of protease inhibitors is being used to simplify the dosing schedule, decrease the pill burden, and improve the efficacy of several of the protease inhibitors. Boosting involves the use of low-dose ritonavir in combination with a second protease inhibitor, also at a reduced dosage. Ritonavir, by inhibiting the cytochrome P-450 system, significantly increases the serum levels of other protease inhibitors that use this elimination pathway. The fixed combination of ritonavir and lopinavir (Kalera) is highly effective and is preferred by many providers, but ritonavir also is commonly prescribed as a boosting agent for atazanavir, fosamprenavir, and indinavir.

There are also several fixed-drug combinations in the NRTI class. These combination pills simply provide a lower pill burden. They include zidovudine and lamivudine (Combivir), emtricitabine and tenofovir-DF (Truvada), abacavir and lamivudine (Epzicom), and zidovudine, lamivudine and abacavir (Trizivir).

Adjunctive therapy—still investigational

Immunomodulatory agents have been considered as potential adjuncts to combination ART. Hydroxyurea has been studied most to date. Through its inhibition of ribonucleotide reductase and possible acceleration of intracellular phosphorylation, hydroxyurea has been shown to enhance the activity of NRTIs in vitro, with the greatest synergy to didanosine [10]. More recent trials have shown no additional benefit in terms of virologic suppression or CD4 T-cell increase and have demonstrated increased toxicity [11–13] manifested as pancreatitis, peripheral neuropathy, and myelosuppression so that use of hydroxyurea as part of an antiretroviral regimen cannot be recommended.

Challenges of antiretroviral therapy

Adverse effects of drugs

The potential for adverse drug effects influences the choice of antiretroviral medications and a patient's ability to continue treatment (Table 3). Reported life-threatening reactions include didanosine-induced pancreatitis, abacavir-related hypersensitivity syndrome, lactic acidosis caused by the use of any of the NRTIs, Stevens-Johnson syndrome secondary to the use of any of the NNRTIs, and liver failure caused by nevirapine [14].

Hypersensitivity syndrome

Abacavir is associated with a potentially fatal hypersensitivity syndrome that can occur in up to 8% of patients. The mechanism and risk factors for this phenomenon are not fully understood, but it is strongly associated with particular HLA haplotypes (HLA-B*5701, HLA-DR7, and HLA-DQ3) [15]. Its nonspecific multisystem presentation and often insidious onset help distinguish abacavir hypersensitivity syndrome from standard allergic reactions. Typically an incremental worsening of symptoms is closely associated with taking additional uninterrupted doses. The most important feature of the hypersensitivity syndrome is the danger associated with interruption followed by rechallenge: patients may develop a severe, multiorgan, life-threatening reaction. In a review of more than 1800 cases, 90% occurred within 6 weeks of drug initiation [16]. Fever, rash, nausea, malaise, fatigue, sore throat, and cough are common symptoms of abacavir hypersensitivity. The rash is usually mild, generalized, and maculopapular and rarely progresses to more severe cutaneous involvement.

Metabolic abnormalities

A number of metabolic abnormalities have been reported in HIV-infected persons, most of which are linked to treatment with antiretroviral agents. Reported metabolic derangements include lactic acidemia, hyperglycemia and insulin resistance, hyperlipidemia, body-fat redistribution (lipodystrophy) [17], and bone abnormalities.

Lactic acidosis

Frank lactic acidosis is an uncommon but serious complication of ART. Mild or asymptomatic lactic acidemia has been reported in 8% to 21% of patients receiving ART [18]; and

symptomatic acidemia occurs in less than 2.5%. The likely mechanism is NRTI-mediated mitochondrial poisoning caused by inhibition of mitochondrial DNA gamma polymerase leading to mitochondrial dysfunction and an increase in endogenous lactate production. Risk factors for the development of lactic acidosis include longer duration of NRTI exposure (especially with stavudine, didanosine [19], and possibly also zidovudine [20]), female gender, and pregnancy. Clinically, nausea, vomiting, and abdominal pain are most frequently reported. Weight loss and anorexia, which may go on for months, are also prominent symptoms of chronic lactic academia. Dyspnea and mental status changes suggest frank acidosis, which, although rare, is associated with high mortality; patients who have serum lactate levels higher than 10 mmol/L have a mortality of approximately 80% [14]. Treatment of symptomatic lactic acidosis should include discontinuation of NRTIs and supportive care. Most patients can be rechallenged successfully with NRTIs less likely to cause lactic academia (eg. abacavir and tenofovir) once the acidosis has resolved [21].

Insulin resistance

Insulin resistance is commonly seen in association with HIV therapy, particularly protease inhibitors. Diabetes mellitus is seen in up to 7% of HIV-infected adults, compared with 0.5% of otherwise healthy control subjects matched for age and body mass index [22]. Proposed mechanisms include a direct effect of protease inhibitors on glucose transport or drug-induced body-fat redistribution (see the later discussion of lipodystrophy) that is associated with increased insulin resistance. In addition to standard therapy as recommended for non–HIV-infected patients who have diabetes, reported treatment strategies include substitution of the protease inhibitor with an NNRTI or abacavir [23–25], although abacavir-based triple nucleoside therapy has been shown to be inferior to protease inhibitor– or NNRTI-anchored treatment and should be avoided.

Hyperlipidemia

Lipid abnormalities are common features of both HIV disease and ART. Reduced levels of high-density lipoprotein and low-density lipoprotein cholesterol and elevated levels of triglycerides were reported in HIV-infected patients before the widespread use of antiretroviral medication [26,27]. The effect of HIV itself on lipid profiles is poorly understood. Protease inhibitors have been implicated as a major cause of dyslipidemia in HIV-infected patients receiving therapy. Protease inhibitors have been observed to increase plasma triglyceride levels, either through increased hepatic synthesis of triglycerides [28–31] or inhibition of apolipoprotein B degradation [32]. Ritonavir has the greatest effect on levels of triglyceride, low-density lipoprotein, and cholesterol [31], whereas nelfinavir and atazanavir have minimal to no effect.

This association with hyperlipidemia has raised concerns about increased risk of cardiovascular disease in HIV-infected patients. One prospective cohort study of 5672 outpatients in nine HIV clinics in the United States reported an increased incidence of myocardial events in patients taking protease inhibitors compared with those not taking protease inhibitors, even after adjusting for smoking, sex, age, diabetes, hyperlipidemia, and hypertension [33]. Similarly, a retrospective study of 23,000 HIV-infected patients enrolled in the multinational Data Collection on Adverse Events of Anti-HIV Drugs study demonstrated a 26% increase in the risk of myocardial infarction for each year of combination ART [34]. A study of 36,000 HIV-infected Veterans Affairs patients, however, found a reduction in the rate of hospital admission for cardiovascular or cerebrovascular disease and a reduction in death from all causes that was associated with ART [35]. Additional data are emerging to support the observation that hyperlipidemia seen in HIV-infected patients treated with ART is one of several factors that increase the risk of development of cardiovascular disease. The benefit of ART, however, is thought to outweigh by far the small additional cardiovascular risk it may confer.

Lipodystrophy

Lipodystrophy, or the fat-redistribution syndrome, has become a prominent long-term complication of ART. Patterns of central fat accumulation in the abdomen, breasts, or posterior neck or peripheral fat wasting in the face, buttocks, and limbs, or both, are typical [36]. Lipodystrophy occurs in 25% to 75% of HIV-infected patients [26,27,37–39].

The exact mechanism of lipodystrophy is poorly understood. Central lipoaccumulation is observed more often in patients taking protease inhibitors and may be related to protease inhibitor-I–associated insulin resistance [27,40].

Fat accumulation has been reported in HIV-infected patients who were not exposed to protease inhibitors, however [37,41]. Lipoatrophy is more closely linked to NRTI exposure [36,42,43], in particular stavudine, and may be caused by NRTI-induced mitochondrial poisoning with subsequent adipocyte death and loss of subcutaneous fat. Risk factors associated with lipodystrophy include older age, low body weight before starting ART, duration of HIV infection, duration and effectiveness of ART, and white race [14,44–47].

Treatment of lipodystrophy remains a challenge: a number of interventions have had limited durable success. Switching from protease inhibitor to protease inhibitor–sparing regimens to reverse fat accumulation may be successful, but results from studies have been mixed [48,49]. Exercise has a limited benefit in reducing fat accumulation [50]. Growth hormone has been shown to reverse fat accumulation [51] but has not gained broad support given the extreme cost, adverse effects, and the need for continued use to sustain benefit. Cosmetic interventions such as injections of collagen-promoting agents or surgical options such as liposuction can reverse the appearance of lipodystrophy, but fat can reaccumulate, frequently within a few months. Preliminary results suggest the need for further study of the insulin-sensitizing agent metformin. In a small randomized, placebo-controlled trial, use of metformin at a dosage of 500 mg two times per day for 3 months was associated with decreased insulin levels and decreased weight as well as a trend toward decreased visceral abdominal fat and subcutaneous abdominal fat [52]. In this study, patients taking metformin did not experience an increase in serum lactate or hepatic aminotransferase levels. The benefit of thiazolidinediones such as rosiglitazone also remains in question; despite benefits on insulin resistance. Three randomized, controlled trials investigating the effects of rosiglitazone in HIV-infected individuals yielded varying results with respect to lipodystrophy. A 24-week study of rosiglitazone showed no benefit in body weight or in total, subcutaneous, or intra-abdominal fat, although some improvement in hepatic steatosis was observed [53]. A 12-week study revealed some improvement in lower-extremity fat assessed by CT scan [54]. The larger 48-week study in patients taking protease inhibitors did not result in improvement of total fat distribution [55]. These studies also describe hypertriglyceridemia and hypercholesterolemia in patients treated with rosiglitazone, making this agent a less attractive option for the treatment of lipodystrophy, particularly for patients who are not insulin resistant.

Goal of long-term viral suppression

Optimal adherence to ART has been shown to be a clear predictor of long-term viral suppression. One prospective study documented virologic failure in 22% of patients with adherence rates of 95% or greater compared with 80% of those with less than 80% adherence [56]. Other studies have confirmed the relationship between adherence and virologic suppression and demonstrated a survival benefit for those with good adherence [57]. Other factors that affect long-term viral suppression are the regimen potency, previous exposure to ART leading to drug resistance, the patient's immune status, drug absorption, and drug–drug interactions that affect the concentration of the antiretroviral medications. A change in therapy should be considered in patients who experience virologic failure or a persistent decline in the CD4 T-cell count, or if there is evidence of clinical deterioration. The choice of a new regimen should take into consideration the patient's prior ART, drug resistance testing, the likelihood of adherence with complex salvage regimens, and the clinical and immunologic stage of the patient's HIV disease.

Drug resistance and resistance testing

Patients may acquire drug-resistant strains of HIV either by transmission of a resistant isolate from another patient or by viral replication in the presence of selective drug pressure. Drug-resistant HIV should be suspected in any patient who has an inadequate response to initial therapy or who develops virologic failure after being suppressed during treatment.

Types of resistance assays

Genotype, phenotype, and virtual phenotype assays are now commercially available to test for HIV drug resistance. Genotypic resistance assays identify specific codon mutations within the reverse transcriptase and protease genes of plasma virus by amplification and sequencing or by use of standardized probes. Results are compared with databases that match particular mutations with drug resistance. Phenotypic resistance assays measure the susceptibility of chimeric viruses that contain the reverse transcriptase and protease genes of the patient's virus spliced into a retroviral

vector that also encodes a marker gene, allowing rapid detection of growth in the presence of varying amounts of antiretroviral medication; the results are reported as the concentration of drug required to inhibit 50% or 90% of viral replication (IC_{50} and IC_{90}, respectively). The strains of HIV identified in the patient are compared with reference strains and reported as the ''fold'' resistance in IC_{50}. Virtual phenotypic resistance testing compares information from a genotypic resistance test with information from a proprietary database containing more than 20,000 genotype–phenotype correlations to predict a resistance phenotype from the genetic sequence of the virus.

There currently is no basis for recommending one assay over the other. Furthermore, in a recent multicenter, randomized trial of treatment-experienced HIV-infected patients experiencing virologic failure, there was no additional clinical benefit from adding phenotypic resistance testing to genotypic resistance testing [58].

All these testing techniques have inherent drawbacks: the tests may fail to detect minority HIV strains that represent less than 20% of the circulating pool of viruses; the sampled strains from the blood may not be representative of strains from other body regions (compartments such as cerebrospinal fluid or seminal fluid); resistance to medications taken in the past may not be evident; and for resistance to be determined, plasma HIV RNA levels typically must be in the range of at least 500 to 1000 copies/mL. Because the tests may miss minority species and not detect nonreplicating archived viruses that may contain resistance mutations, they cannot predict with certainty which drugs will work. Nevertheless, several studies have shown that patients who undergo resistance testing in the setting of virologic failure have better virologic outcomes than those who do not undergo resistance testing [59,60].

Indications for resistance testing

The DHHS guidelines recommend resistance testing for patients who experience virologic failure during ART; for patients with a suboptimal suppression of viral load after starting therapy; for patients who have acute HIV infection who are considering treatment immediately or in the future, because of the known transmission of drug-resistant HIV variants; and for patients with chronic HIV infection prior to initiation of ART because studies suggest that baseline testing may be cost-effective in identifying patients at risk of suboptimal virologic suppression [61]. Virologic failure is constituted by any one of the following three events:

1. A decrease in HIV RNA of less than 1.0 $\log_{10}$ by week 4 of after starting ART
2. A failure to suppress the level of HIV RNA to less than 400 copies/mL at 24 weeks or 50 copies/mL within 48 weeks of starting or changing therapy
3. Repeated detection of a high level of HIV RNA in plasma after initial suppression to less than 50 copies/mL

Summary

Because the field of ART continues to change at a rapid pace, clinicians need easy access to updated resources. A list of online resources is given in the introductory article in this issue.

Improvements in convenience, tolerability, and toxicity of antiretroviral medications have narrowed the gap between potency and simplicity in combination regimens in recent years. No matter how simple the regimens become, a number of concerns remain associated with their use, particularly because individuals taking these regimens are living longer. Also, adherence will always remain a challenge in this setting, underscoring the importance of individualizing treatment decisions to maximize the likelihood of a durable response.

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