INFECTIOUS DISEASES I

PSAP

HIV INFECTION: NEW AND CHALLENGING ISSUES FOR MANAGING A CHRONIC DISEASE

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Learning Objectives

1. Identify and assess clinically significant drug interactions between anti-retroviral agents and concomitant drug therapy.
2. Demonstrate an understanding of anti-retroviral drug interaction mechanisms and appropriate dose adjustment or alternative therapeutic recommendations.
3. Analyze anti-retroviral treatment options for treatment-experienced patients and distinguish the advantages and disadvantages between each agent.
4. Demonstrate the relationship between anti-retroviral therapy and cardiovascular disease, including management and treatment of dyslipidemia, in human immunodeficiency virus (HIV)–infected patients.
5. Evaluate the management and treatment for patients coinfected with hepatitis C virus and HIV.

Introduction

In the United States, more than 1 million people are infected with human immunodeficiency virus (HIV), and it is estimated that 25% of infected individuals are undiagnosed and unaware of their status. Despite the overwhelming numbers, significant achievements have been made, none more important than the dramatic decline in morbidity and mortality because of the introduction of highly active anti-retroviral therapy (HAART). Most patients with HIV infection now require management strategies similar to other chronic diseases. However, management of HIV infection using anti-retroviral therapy has brought new and difficult challenges to clinicians. This chapter will delineate some of the medical issues that clinicians who care for patients with HIV infection confront or will need to address in the future. Topics discussed in this section will be HAART-associated drug interactions, anti-retroviral treatment options for HIV treatment–experienced patients, management of HIV treatment–associated dyslipidemia, and evaluation and management strategies for hepatitis C virus (HCV) coinfection.

Drug Interactions

Drug interactions have been associated with HIV treatment since the introductions of protease inhibitors (PIs) 10 years ago and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) shortly thereafter. Most drug interactions associated with PIs and NNRTIs are mediated by either hepatic enzyme inhibition or induction. Other mechanisms known to cause fluctuations in anti-retroviral drug concentrations are efflux transporters (P-glycoprotein) and uptake transporters (organic anion transporters) located in the gastrointestinal tract lumen and other tissues, drug-food interactions, and gastric acidity. Pharmacists' recognition of drug interactions plays a significant role in HIV treatment success or failure. Treatment of HIV infection requires lifelong anti-retroviral therapy; in addition, many patients require concomitant drugs for treating other comorbid conditions. Polypharmacy is, therefore, unavoidable and inevitable and provides a platform for pharmacists to have a significant impact on patient care.

Ritonavir

Ritonavir is a PI that is typically coadministered with other PIs to enhance their pharmacologic effects. This dosing strategy is commonly referred to as *ritonavir-boosted PIs.* Ritonavir is a potent cytochrome P450 (CYP) 3A4 inhibitor that impedes the metabolism of coadministered PIs, resulting in their significantly higher plasma concentrations. Higher plasma concentrations of coadministered PIs caused by the addition of low-dose ritonavir (100–200 mg) to virtually all PI-based regimens result in improved antiviral efficacy, reduced pill burden, decreased viral resistance, and less frequent dosing. However, this antiviral benefit can be problematic for patients taking other drugs metabolized by CYP isoenzymes. The most significant PI-associated drug interactions are due to ritonavir. Ritonavir has an extensive list of potential drug interactions and contraindicated drugs that clinicians should recognize (Table 1-1). Table 1-1 is not all-inclusive; other significant ritonavir-associated drug interactions are discussed in this chapter. Ritonavir drug interactions can be difficult to predict because not

Abbreviations in This Chapter

AIDS	Acquired immunodeficiency syndrome
AUC	Area under the concentration-time curve
CCR5	Human chemokine coreceptor-5
Cmin	Trough plasma concentration
CVD	Cardiovascular disease
CYP	Cytochrome P450
HAART	Highly active anti-retroviral therapy
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
LDL	Low-density lipoprotein
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PDE5	Phosphodiesterase enzyme 5
PIs	Protease inhibitors
RNA	Ribonucleic acid
TORO	T-20 versus optimized background regimen only

only does ritonavir affect multiple CYP isoenzymes (primarily inhibition and, to a lesser degree, induction), but the magnitude of effect can also be dose-dependent. Ritonavir drug interactions should be evaluated for clinical significance, availability of alternative agents, appropriate change in dosage (if applicable), and therapeutic benefit of the interacting drug. Clinicians caring for patients with HIV infection require readily accessible and current ritonavir drug-drug interaction data.

Non-nucleoside Reverse Transcriptase Inhibitors

The NNRTIs efavirenz and nevirapine have significant drug interactions with antifungal agents. At standard doses, efavirenz decreases the AUC of voriconazole by 77%, and voriconazole increases the efavirenz AUC by 44%. Because of this interaction, when efavirenz is used in combination with voriconazole, the dosage of voriconazole should be increased to 400 mg twice daily and the dosage of efavirenz should be reduced to 300 mg daily. In addition, fluconazole increases the AUC of nevirapine by 100%, so this combination should be used cautiously. No interaction occurs between fluconazole and efavirenz.

Gastric Acid–Reducing Agents

Gastrointestinal adverse effects associated with anti-retroviral drugs are common. The availability of over-the-counter histamine$_2$-receptor antagonists and proton pump inhibitors to treat these symptoms has made these agents popular among patients with HIV infection. Atazanavir exhibits pH-dependent solubility, and absorption is inadequate in a nonacidic environment. Omeprazole significantly decreases the trough plasma concentrations (Cmin) and area under the concentration-time curve (AUC) of atazanavir (78% and 76%, respectively). The effect that omeprazole has on atazanavir can be extrapolated to all proton pump inhibitors and cannot be sufficiently overcome with the addition of ritonavir. The reduced concentration poses a significant risk to atazanavir's antiviral activity. Proton pump inhibitors are not recommended with atazanavir, regardless of whether ritonavir is coadministered.

Histamine$_2$-receptor antagonists also decrease atazanavir Cmin but to a lesser extent (approximately 50%). This reduction can be overcome by two different dosing strategies. Higher atazanavir concentrations can be achieved with the coadministration of ritonavir (atazanavir 300 mg plus ritonavir 100 mg daily); alternatively, if ritonavir is not used, the oral administration of atazanavir (400 mg daily) can be temporally separated from the histamine$_2$-receptor antagonist by 10–12 hours. Pharmacists need to be diligent about educating patients who are taking atazanavir regarding this significant drug interaction. For patients who require a proton pump inhibitor, other PIs can be used, as recommended by the U.S. Department of Health and Human Services HIV treatment guidelines (lopinavir/ritonavir and fosamprenavir/ritonavir).

Some clinicians who treat HIV infection have suggested that the use of therapeutic drug monitoring to measure drug concentrations of atazanavir would be appropriate; however, this method has yet to be validated for routine clinical practice. The use of therapeutic drug monitoring of anti-retroviral agents continues to remain in clinical trials. For therapeutic drug monitoring to be useful in clinical practice, procedures for appropriate sample collection, analytic methods, and interpretation of drug concentration data need to be standardized and validated; in addition, third-party payers for these tests need to be identified.

Opioids

Opioid dependence is a common problem for patients with HIV infection. These closely related epidemics are resulting in growing numbers of patients receiving treatment for both. Opioid agonist therapy is the most effective treatment for opioid-dependent patients. Methadone is the principal opioid agonist used for the treatment of opioid dependence; it undergoes hepatic metabolism by multiple CYP enzymes (CYP 3A4, CYP 2B6, and CYP 2D6). Efavirenz and nevirapine induce methadone metabolism through CYP 3A4 and, probably, CYP 2B6, resulting in numerous reports of opiate withdrawal when either of these NNRTIs is initiated. Studies have shown a significant decrease in methadone AUC (40% to 60%) in patients taking efavirenz or nevirapine, which required a median methadone dose increase of 13% to 35% to treat these withdrawal symptoms.

Methadone pharmacodynamics are characterized by large interindividual variability. The onset of symptoms of opioid excess or withdrawal is highly variable, which limits the clinical application of monitoring methadone plasma concentrations. Instead, clinical management includes the evaluation of objective signs and subjective symptoms of opiate withdrawal and individualized dose titration when necessary. For example, clinicians familiar with the clinical

Table 1-1. Drugs That Should Not Be Coadministered with Ritonavir[a]

Drug Class	Drug	Alternative Agent	Clinical Comment	Mechanism
α_1-Adrenorecepter antagonist	Alfuzosin	Doxazosin	Contraindicated potential for serious adverse reactions such as hypotension	CYP 3A4 inhibition
Antiarrhythmics	Amiodarone, bepridil,[b] flecainide, propafenone, quinidine	No	Contraindicated—all are likely to result in ↑ plasma concentration, increasing risk of arrhythmias or other serious adverse event	CYP 3A4 inhibition
Non-sedating antihistamines	Astemizole,[b] terfenadine[b]	Fexofenadine, loratadine	Contraindicated—potential for life-threatening arrhythmias	CYP 3A4 inhibition
Ergot derivatives	Ergotamine, ergonovine, dihydroergotamine, methylergonovine	Sumatriptan	Contraindicated—potential for serious adverse events, such as vasospasm, acute ergot toxicity, and ischemia	CYP 3A4 inhibition
Gastrointestinal motility agents	Cisapride[b]	Metoclopramide	Contraindicated— potential for life-threatening arrhythmias	CYP 3A4 inhibition
HMG-CoA reductase inhibitors	Lovastatin, simvastatin, rosuvastatin	Pravastatin, atorvastatin[c]	Contraindicated— substantial ↑ in plasma concentration can lead to myopathy, including rhabdomyolysis	CYP 3A4 inhibition
Sedatives/Hypnotics	Midazolam, triazolam, diazepam	Lorazepam, oxazepam, temazepam	Contraindicated—↑ in plasma concentration can prolong sedation or respiratory depression	CYP 3A4 inhibition
Antipsychotics[d]	Olanzapine, haloperidol, risperidone, pimozide	Ziprasidone (partially metabolized by CYP 3A4)	53% ↓ in AUC Expected ↑ in AUC Contraindicated—potential for life-threatening arrhythmias	CYP 1A2 induction CYP 2D6 inhibition CYP 2D6 inhibition CYP 3A4 inhibition
Steroids (inhaled/nasal)	Fluticasone, budesonide	Beclomethasone	Not recommended, unless the benefits outweigh the risk of systemic corticosteroid side effects; corticosteroid concentration	CYP 3A4 inhibition
Antidepressant	Trazodone		Trazodone AUC ↑ 2.5-fold; adverse effects such as nausea, dizziness, hypotension, and syncope have been reported	CYP 3A4 inhibition
Antifungals	Voriconazole	Fluconazole, itraconazole	Voriconazole AUC ↓ 82% and 39% when coadministered with ritonavir 400 mg and 100 mg two times/day, respectively. Avoid coadministration	CYP 2C9/2C19 induction

[a]Dosage of ritonavir in pharmacokinetic drug interaction studies has ranged from 100 mg two times/day to 600 mg two times/day.
[b]Agents removed from U.S. market; these may still be available from other sources or in other countries.
[c]Atorvastatin AUC is increased 6-fold; recommend starting with 10 mg and titrating to effect.
[d]Excluding pimozide, all other atypical antipsychotics can be used cautiously with ritonavir.
AUC = area under the curve; CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

opiate withdrawal scale can monitor resting pulse rate, sweating, restlessness, runny nose or tearing, gastrointestinal upset, tremor, and irritability as indicators of opiate withdrawal and recommend a dose change, if clinically indicated. Patients on methadone who are ready to initiate nevirapine or efavirenz should be educated on the subjective and objective symptoms of opioid withdrawal. Diligence in monitoring for opioid withdrawal will prevent unnecessary treatment discontinuation and improve patient quality of life. Dose adjustment of methadone may be required for the first 4 weeks when hepatic enzyme induction is likely to occur.

Protease inhibitors have a mixed effect on methadone metabolism; some studies show decreases, whereas others show increases in methadone plasma concentrations. In either case, the interaction with PIs appears to have little clinical significance, except for tipranavir, which decreases methadone AUC by 50%.

Buprenorphine is a partial μ-receptor agonist that is approved for treating opioid dependence and is equivalent in efficacy to methadone. Buprenorphine has advantages over methadone for patients with HIV infection because it is the first opioid for treating opioid dependence available in general medical settings. This availability allows patients with HIV infection to be treated for their substance dependence and medical illness from the same medical provider (providers are required to have an "X" replacing the first letter of their Drug Enforcement Administration number to prescribe buprenorphine). Candidates for buprenorphine should have all opioid analgesics (including methadone) tapered to discontinuation at least 24–48 hours before initiating buprenorphine; otherwise, withdrawal symptoms could be precipitated.

Buprenorphine is metabolized to an active metabolite (norbuprenorphine) primarily by CYP 3A4 and CYP 2C8. Limited data exist on drug interactions between buprenorphine and anti-retroviral agents. Efavirenz decreases buprenorphine AUC and norbuprenorphine AUC by 49% and 71%, respectively. Despite the magnitude of change, no significant pharmacodynamic effects were observed in study participants. This unexpected result is probably because of the high binding affinity buprenorphine has for the opiate μ-receptor, preventing withdrawal symptoms. Drug interaction data between buprenorphine and PIs need to be collected before buprenorphine is prescribed to patients with HIV infection who are treated with PIs.

Anticonvulsants

Anticonvulsant drugs are used to treat seizures, which can occur with many HIV-associated central nervous system opportunistic infections; in addition, anticonvulsants are used to treat patients with HIV infection who also have bipolar disorder and neuropathic pain. Older anticonvulsants (i.e., phenobarbital, carbamazepine, and phenytoin) are well documented to cause CYP enzyme induction and can significantly lower the plasma concentrations of many hepatically metabolized drugs. Phenytoin is not recommended for coadministration with PIs or NNRTIs because of enzyme induction that could result in virologic failure. A bidirectional interaction occurs between phenytoin and lopinavir/ritonavir, by which lopinavir Cmin is reduced by 46% and phenytoin AUC decreases by 31%. The proposed mechanism of reduction in lopinavir concentrations is CYP 3A4 induction by phenytoin; lopinavir/ritonavir induces CYP 2C9, which explains the reduction in phenytoin concentrations. Other anticonvulsants, such as gabapentin and levetiracetam, are eliminated renally and can replace phenytoin for some seizure types. Valproic acid has a low propensity to affect CYP isoenzymes and can be coadministered with PIs and NNRTIs.

Rifamycins

Rifamycins cause CYP hepatic enzyme induction and have significant interactions with PIs and NNRTIs. Rifamycins differ in potency as CYP 3A4 inducers, with rifampin being the most potent, rifapentine intermediate, and rifabutin the least potent. Rifapentine, a long-acting rifamycin, is not recommended for treatment of tuberculosis in patients with HIV infection because of an unacceptably high rate of relapse with organisms that have acquired resistance to rifamycins. Rifampin is contraindicated with all PIs, with the possible exception of saquinavir/ritonavir (400 mg/400 mg twice daily); however, this dosage is seldom used in clinical practice. Data from the current recommended dosage of saquinavir/ritonavir (1000 mg/100 mg twice daily) coadministered with rifampin showed higher-than-expected liver toxicity, and this combination should be avoided. Non-nucleoside reverse transcriptase inhibitors are also not recommended to be coadministered with rifampin; however, there are data supporting the use of standard doses of nevirapine and efavirenz with rifampin. A few small pharmacokinetic studies have shown variable reductions in efavirenz plasma concentrations when coadministered with rifampin, which support an alternative recommendation to increase the efavirenz dose to 800 mg daily.

When a rifamycin is necessary, rifabutin is the drug of choice. Unlike rifampin, rifabutin is a substrate of CYP 3A4 and is another example of bidirectional drug interaction when used with anti-retroviral drugs. Numerous pharmacokinetic studies have provided dosing recommendations for rifabutin when used with PIs and NNRTIs. However, the bidirectional drug interaction between rifabutin and PIs and NNRTIs is problematic, because evidence from recent reports has shown the development of acquired rifamycin resistance. Recent pharmacokinetic data have suggested that higher doses of rifabutin are necessary, and revised dosing recommendations should be forthcoming. Until those recommendations are available, rifabutin should be reduced to 150 mg every other day when coadministered with all ritonavir-boosted PIs and unboosted atazanavir. For all other PIs not coadministered with ritonavir, the rifabutin dose should be reduced to 150 mg daily. Rifabutin should be increased to 450 mg daily or 600 mg three times weekly when coadministered with efavirenz. The dosage increase is because of CYP 3A4 enzyme induction by efavirenz. No dose adjustment is necessary when rifabutin is coadministered with nevirapine.

Phosphodiesterase Enzyme 5 Inhibitors

Erectile dysfunction has not been well studied in patients with HIV infection but is a common occurrence in observational studies of this population. The prevalence of sexual dysfunction and hypogonadism in men who receive

HAART has been reported to be as high as 20%. Regardless of the etiology, the availability of phosphodiesterase enzyme 5 (PDE5) inhibitors to treat male erectile dysfunction has given patients with HIV infection the opportunity to seek treatment.

There are three agents currently available for the treatment of male erectile dysfunction (i.e., sildenafil, tadalafil, and vardenafil). Sildenafil metabolism is primarily mediated by CYP 3A4 (major route) and 2C9 (minor route). Coadministration of ritonavir (500 mg twice daily) and sildenafil (100 mg single dose) resulted in an 11-fold increase in sildenafil AUC. Coadministration is not recommended with ritonavir, but if coadministration occurs, sildenafil should not exceed 25 mg in a 48-hour period. Tadalafil is metabolized predominantly by CYP 3A4. Ritonavir (200 mg twice daily) increased tadalafil (20 mg single dose) AUC by 2-fold, which led to the recommendation that the tadalafil dose not exceed 10 mg and not be taken more frequently than every 72 hours. Although specific drug interactions have not been studied, other PIs would likely increase tadalafil exposure. Vardenafil is metabolized by CYP 3A4 and 2C9. Coadministration of ritonavir (600 mg twice daily) and vardenafil (5 mg single dose) increased vardenafil AUC by 49-fold and prolonged the half-life to 26 hours. Low-dose ritonavir has not been studied with vardenafil and should be used with caution. If vardenafil is prescribed with PIs, the dose should be reduced to 2.5 mg every 72 hours with increased monitoring for side effects.

Clinicians need to be very cautious when prescribing PDE5 inhibitors with PIs because of the potential for toxicity. Patients should be educated about adverse effects such as visual disturbances, prolonged erection, headache, syncope, hypotension, and chest pain. These drugs should be avoided in patients who have HIV infection and cardiovascular disease (CVD). In addition, clinicians who prescribe PDE5 inhibitors for patients taking NNRTIs should be aware that enzyme induction will likely result in decreased PDE5 inhibitor drug concentrations.

Herbal Therapies and Dietary Supplements

The use of herbal therapies and dietary supplements is particularly common among patients with HIV infection. Problems occur because clinicians are often unaware of herbal product use by patients, are unaware of their therapeutic claims, and seldom inquire if patients are taking these products. Pharmacists should be cognizant that patients with HIV infection who have different cultural beliefs may seek treatment remedies from nontraditional medical providers. Surveys from patients infected with HIV have demonstrated widespread herbal and supplement use (25% to 100% in selected cohorts); therefore, pharmacists need to be a reliable source of information about these products for patients and providers. This goal is not easy to achieve because of multiple factors. For example, there is a paucity of data regarding potential drug interactions between herbal therapies and anti-retroviral agents. It is unlikely that clinicians can expect herbal drug interaction studies with contemporary anti-retroviral drugs because of numerous study limitations (e.g., unpurified product, questionable effective doses, product variability).

Pharmacists should assess risk and benefit when consulting patients about herbal therapies. The risk-benefit assessment must include potential side effects and drug interactions of herbal therapies, which is usually contrary to patient beliefs and public perception regarding the safety of these products. For instance, St. John's wort causes CYP 3A4 hepatic enzyme induction and decreases indinavir plasma concentrations by 50%. A general recommendation is that PIs and NNRTIs not be coadministered with St. John's wort. Limited data from other herbal products have shown that goldenseal, kava kava, and black cohosh can inhibit CYP P450 enzymes, whereas garlic supplements may induce CYP 450 enzymes. These agents should be used cautiously with anti-retroviral therapy.

To assess risk and benefit satisfactorily for patients with HIV infection who are taking or about to initiate herbal therapies, the pharmacist should obtain a complete and thorough drug history. This should include over-the-counter drugs, alcohol or illicit drug use, herbal products, and homeopathic and cultural remedies. The drug history should be obtained in a nonjudgmental manner, and the patient should be reassured that the majority of commonly used herbal products are probably safe to take with anti-retroviral agents.

Anti-Retroviral Therapy for Treatment-Experienced Patients

Treatment recommendations for patients with HIV infection are constantly evolving. The majority of treatment recommendations are based on data from controlled clinical trials in patients who are treatment naïve. Current HIV treatment models use combination therapy to achieve maximal and durable viral suppression. Increased potency of newer agents and improved adherence caused by the coformulation of existing agents has resulted in improved clinical outcomes. Other recent studies have shown that HIV infection requires lifelong therapy. The notion that patients could discontinue anti-retroviral therapy based on CD4 T-lymphocyte counts (structured treatment interruption) was dismissed when patients who did so were shown to have unexpected disease progression and death. Lifelong treatment for HIV infection is the standard of care, but it comes at a significant financial cost (expected cost per quality-adjusted life-year gained ranges from $7000 to $28,000; about 75% of the cost is attributed to anti-retroviral drugs) and often results in the emergence of drug-resistant virus.

The long-term use of anti-retroviral therapies is limited by the development of resistance and toxicity associated with many of these agents. Multidrug-resistant HIV infection and cross-resistance to agents within a pharmacological class limit treatment options and create the need for new agents and new classes of anti-retroviral drugs. The availability of enfuvirtide, tipranavir, and darunavir has given clinicians and patients renewed optimism for treating drug-resistant HIV because these drugs are more potent and durable than those previously available. Besides darunavir, tipranavir, and enfuvirtide, clinicians anticipate the arrival of another new agent (etravirine) that will add to the treatment

Table 1-2. Characteristics of Next-Generation Anti-Retroviral Agents

Drug	Class	Availability	Dosage	Half-life (hours)	Metabolism	Comments
Etravirine	NNRTI	Expanded Access Program, Phase III Clinical Trials	200 mg two times/day. Administer with food (bioavailability ↑ 3-fold)	30–40	CYP 3A4 and 2C isoenzymes	Drug interactions likely with other CYP 3A4 metabolized drugs. OK to administer with maraviroc, darunavir, lopinavir/ritonavir. Resistance to etravirine requires multiple mutations. Activity ↓ if 3 or more baseline NNRTI mutations. No data in pregnancy
Raltegravir	Integrase inhibitor	FDA approved	400 mg two times/day with or without food	7–12	Glucuronidation (UGT1A1)	Does not require coadministration with ritonavir. No short-term changes in cholesterol or triglycerides. No data in pregnancy. Need additional resistance data
Maraviroc	CCR5-antagonist	FDA approved	150 mg two times/day when coadministered with CYP 3A4 inhibitors (except for tipranavir/ritonavir) 300 mg two times/day when coadministered with other drugs, including tipranavir/ritonavir 600 mg two times/day when coadministered with CYP 3A4 inducers (without a CYP 3A4 inhibitor)	13	CYP 3A4 P-glycoprotein substrate	Antagonism not expected when used with other anti-retrovirals, including enfuvirtide. Only for patients who are CCR5 positive as determined by a coreceptor tropism assay

CCR5 = human chemokine coreceptors R5; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; NNRTI = non-nucleoside reverse transcriptase inhibitor; UGT1 = uridine diphosphate-glycuronose-transferase 1.

armamentarium against drug-resistant virus (Table 1-2). Two other agents, maraviroc and raltegravir, were recently approved for treatment of drug-resistant HIV. The clinical role each agent will provide is not yet clearly defined, but preliminary data from ongoing trials are laying the foundation for clinical application.

Enfuvirtide

One of the most significant achievements in the past few years has been the improved virologic and immunologic response in treatment-experienced patients with HIV infection. The initial breakthrough came with the development of a new class of agents, HIV entry inhibitors, of which enfuvirtide (more specifically, a fusion inhibitor) was the first agent licensed in the United States. *Entry inhibitor* is a broad description for agents that impede different mechanisms by which HIV gains cellular entry. From a therapeutic perspective, entry is an attractive point to impede the viral life cycle because drug activity is independent of intracellular processes. The HIV entry process has three discrete steps: attachment, coreceptor binding, and fusion. Enfuvirtide is a synthetic 36–amino acid peptide inhibitor of HIV envelope glycoprotein 41–mediated fusion between HIV and the target cell membrane. In other words, enfuvirtide blocks the entry of viral particles into CD4 T lymphocytes by preventing the fusion of the viral membrane with the host cell membrane.

Enfuvirtide was the first anti-retroviral agent to show significant virologic and immunologic response in treatment-experienced patients. The two T-20 (enfuvirtide) versus optimized background regimen-only studies (TORO 1 and TORO 2) were pivotal and laid the framework by which subsequent clinical studies would be designed for treatment-experienced patients with HIV infection. The methodology was specific in that patients were randomized to receive either optimized background therapy based on HIV resistance tests or optimized background therapy plus enfuvirtide. These treatment arms enabled patients to receive as many active drugs as possible as part of their study regimen, with or without enfuvirtide. Results from

these studies showed that patients who received enfuvirtide had significantly greater viral load reductions than the comparator arm. These results provided confirmation that the addition of enfuvirtide further enhanced the viral load reduction produced by an optimized treatment regimen.

Enfuvirtide should be reserved for patients in whom cumulative HAART exposure has resulted in multi-class HIV drug resistance; however, the role of enfuvirtide in clinical practice is not well delineated. Enfuvirtide possesses some unique characteristics, such as a target site that results in the absence of cross-resistance with other approved anti-retroviral agents, potent antiviral activity, a low incidence of systemic toxicity, and the lack of drug-drug interactions with PIs or NNRTIs. Despite these advantages, enfuvirtide has significant limitations that affect its use. Subcutaneous injections twice daily and injection site reactions introduce a dimension of patient training and support that is essential for long-term use.

In the management of treatment-experienced patients, the potential clinical consequences of using enfuvirtide as the only active agent in a proposed regimen must be weighed against maintaining the current regimen and waiting until two or more active drugs can be initiated. The risk of maintaining the current regimen when the patient has a detectable viral load is that the acquisition of additional viral mutations could decrease the activity of new agents in development. The risk of using enfuvirtide, if it is the only active agent in the regimen, is the likelihood of developing mutations in the glycoprotein 41 motif, resulting in enfuvirtide resistance. Because of the cost of enfuvirtide (about $20,000/year), there are insufficient data to warrant continued use when enfuvirtide resistance has developed. The recent addition of two new PIs (tipranavir and darunavir), which have excellent activity against PI-resistant virus, will help prevent enfuvirtide from being used as the only active agent. However, the clinical use of enfuvirtide will soon be challenged by the development of new agents representing new anti-retroviral therapeutic classes. These newer agents will likely be preferred by patients and clinicians because they are administered orally, are well tolerated, and are less expensive than enfuvirtide.

Tipranavir

Tipranavir is the first PI approved in the United States specifically for the treatment of PI-experienced patients. Tipranavir was in clinical development for years before it became available as a therapeutic agent. Part of the delay was to identify a drug regimen that would achieve antiviral concentrations; tipranavir must be coadministered with ritonavir 200 mg twice daily. Tipranavir studies were similar in design to enfuvirtide studies. PI-experienced patients were randomized to optimized background therapy with or without ritonavir-boosted tipranavir, based on HIV resistance tests. Results from these studies showed excellent activity against PI-resistant virus, and tipranavir performed statistically better than the comparator arm. The patients who received enfuvirtide in the tipranavir arm, not surprisingly, had the greatest response.

One significant limitation of tipranavir is its association with drug-induced hepatotoxicity. In clinical trials, about 6% of patients developed liver transaminases increases five times greater than normal values, and cases of hepatic decompensation were reported. This led to a warning that tipranavir is not recommended for patients coinfected with hepatitis B or C viruses. Tipranavir also has numerous significant drug interactions, as well as a black box warning for intracranial hemorrhage. For these reasons, the initial enthusiasm for tipranavir appears to be subsiding.

Darunavir

Darunavir is a PI that became available shortly after tipranavir and showed impressive antiviral activity and immunologic response in treatment-experienced patients. The clinical trials for darunavir were similar in design to those for tipranavir and enfuvirtide. Treatment outcomes were also similar to those studies. Patients who had the greatest number of active agents in their treatment regimen had superior efficacy. Of patients who received darunavir plus enfuvirtide (two active agents), an unprecedented 62% achieved an HIV viral load reduction of at least 1.0 log from baseline, and 40% had a viral load below the limits of detection (less than 50 copies/mL). These impressive results have not been observed in previous studies of treatment-experienced patients. Besides potent antiviral effects, darunavir requires less ritonavir than tipranavir (100 mg twice daily compared with 200 mg twice daily), is well tolerated, and appears to have fewer drug interactions than tipranavir. All of these characteristics make darunavir an excellent treatment option for PI-experienced patients. Darunavir is not without its limitations: patients who have significant PI resistance, especially with certain key mutations, are less likely to respond; study results are based on short follow-ups (24 weeks); and the darunavir resistance profile is still incomplete.

Maraviroc

Maraviroc is an entry inhibitor that is different from enfuvirtide because it blocks viral entry at a different step of the process. After HIV attachment to the CD4 receptor, HIV envelope glycoprotein 120 undergoes a conformational change that facilitates binding to a second chemokine coreceptor. Maraviroc is a noncompetitive antagonist (inhibitor) of human chemokine coreceptor-5 (CCR5). Maraviroc inhibits HIV glycoprotein 120 binding to CCR5, which is one of two coreceptors that HIV uses to gain cellular access. Because of this blockage, HIV is unable to enter the cell and begin the viral replication cycle. This has several possible advantages. Maraviroc prevents HIV entry, so it does not require intracellular transport or metabolism; and, by blocking viral entry, it inhibits the first step of the viral life cycle.

Inhibitors of CCR5 are not without potential complications. Because CCR5 is a naturally occurring cellular receptor, blocking this receptor might inhibit normal cellular biological functions. One CCR5 inhibitor is no longer in development because of hepatotoxicity, and another agent in clinical development may be associated with increased risk of lymphoma. Neither of these adverse events has been observed with maraviroc. A small percentage of the population lacks the CCR5 gene and is completely deficient of this coreceptor; yet they lead completely normal, healthy lives and are essentially immune to HIV. Adverse

effects that are associated with maraviroc have been mild to moderate and produce few treatment discontinuations. Maraviroc is metabolized by CYP 3A4, and dose adjustment may be necessary if CYP 3A4 inhibitors or inducers are given concomitantly.

HIV has the ability to use two chemokine coreceptors (CCR5 and CXCR4) located on the cell membrane surface; this facilitates viral entry into the host cell. Maraviroc is useful only in those patients whose virus targets the coreceptor CCR5 (*CCR5-tropic* is another term to describe the affinity or phenotype of the coreceptor the virus uses). There is concern that blocking CCR5 could encourage the emergence of HIV strains that use CXCR4 coreceptor (CXCR-tropic), which may promote more rapid disease progression and loss of CD4 T lymphocytes. Initial studies show that maraviroc treatment resulted in selection for CXCR4 virus in patients with pre-existing CCR5/CXCR4 (dual/mixed)-tropic virus that was not detected by the tropism assay. *Dual/mixed-topic* describes a virus that has the ability to use both coreceptors. Although maraviroc was ineffective virologically in this patient population, CD4 T lymphocytes actually increased. One disadvantage of maraviroc is the added laboratory cost of the tropism assay necessary to determine which viral coreceptor the virus uses. Another potential problem is assay sensitivity: reports from initial viral tropism analysis have shown that about 8% to 10% of patients reported as CCR5-tropic were, in fact, CCR5/CXCR4 dual/mixed-tropic. In this instance, maraviroc would appear appropriate; however, it is not likely that these patients with a dual/mixed-tropic virus would receive any therapeutic benefit.

Raltegravir

Raltegravir (formerly known as MK-0518) is a compound that represents a new class of agents, the HIV integrase inhibitors. Raltegravir targets HIV integrase, which is the virus-specific enzyme responsible for the integration of HIV into the human genome. This unique mechanism of action has promising clinical benefit, as demonstrated by its potent antiviral activity against drug-resistant virus.

Raltegravir is metabolized primarily through glucuronidation. It is not a substrate, inhibitor, or inducer of CYP isoenzymes, which implies that interactions with other drugs metabolized by these enzymes are unlikely. Raltegravir appears safe to coadminister with NNRTIs and PIs, although additional pharmacokinetic studies are needed. Adverse effects reported from short-term studies were mild to moderate (headache, dizziness, abdominal discomfort, and fatigue) and were observed with similar frequency in the placebo arms, but longer follow-up data are needed to better characterize raltegravir's adverse effect profile.

The promising effectiveness and excellent tolerability of raltegravir suggest that it has the potential to become an important component of treatment regimens for patients harboring multidrug-resistant virus and who have limited treatment options. One clinical issue that needs further evaluation is the identification of HIV integrase mutations and the significance these mutations have on the activity of raltegravir. Viral resistance to raltegravir is relatively unknown, and few laboratories have the capability to sequence the HIV integrase gene. Viral resistance testing will presumably be necessary if a patient is not responding to raltegravir and will be an additional laboratory expense that third-party payers will need to cover.

Etravirine

Etravirine (formerly known as TMC-125) is an NNRTI that has antiviral activity against NNRTI-resistant virus. The primary limitation of available NNRTIs is the low barrier to resistance that the virus has to overcome. Before the development of etravirine, the only requirement to render NNRTIs useless was a single point mutation in the HIV reverse transcriptase gene. Etravirine is structurally unique from other NNRTIs because it can adapt to changes (i.e., mutations) in the NNRTI binding pocket. This "wiggling" effect allows it to inhibit HIV reverse transcriptase and escape the effects of NNRTI drug-resistant mutations. With most people with HIV infection in the developed and developing world on NNRTI-based regimens, the availability of etravirine to treat efavirenz and nevirapine resistance has the potential to fill a major void.

Etravirine is metabolized by CYP 3A4 and 2C isoenzymes; it induces CYP 3A4 and is eliminated as glucuronide conjugates. Additional pharmacokinetic studies are necessary to determine optimal dosing if coadministered with PIs. Results from initial clinical studies with short-term follow-up characterize etravirine as a safe and well-tolerated drug. The most common adverse effects reported, which were mild or moderate, were diarrhea, nausea, headache, insomnia, and rash. One advantage is that the incidence of associated central nervous system side effects is lower with etravirine than with efavirenz, but pancreatitis and hepatotoxicity have been reported; these will require further evaluation and monitoring.

Another issue is whether etravirine is potent enough to treat PI treatment–naïve patients who have developed resistance to a prior NNRTI-based regimen. One study showed that PI-naïve patients who had NNRTI resistance were more likely to achieve an undetectable HIV viral load on a ritonavir-boosted PI regimen than on an etravirine-based regimen. The optimal strategy to treat patients who have developed NNRTI resistance has not been determined; it may include combining etravirine with ritonavir-boosted PI to achieve the most potent and durable viral load reduction, but this needs further evaluation.

Cardiovascular Disease and HIV

In 1993, acquired immunodeficiency syndrome (AIDS) was the leading cause of death in men between the ages of 25 and 44 years; however, since the introduction of HAART and the subsequent decline in mortality, death caused by CVD is now higher than AIDS in the same age group. The benefits derived from anti-retroviral therapy and the significance placed on viral suppression and CD4 T-lymphocyte recovery are more important than the cardiovascular risk factors in the AIDS population, but cardiovascular risk factors should not be overlooked. This basic tenet of primary care is challenging for HIV patient care providers because many of the drugs that brought about the reduction in AIDS mortality can cause dyslipidemia,

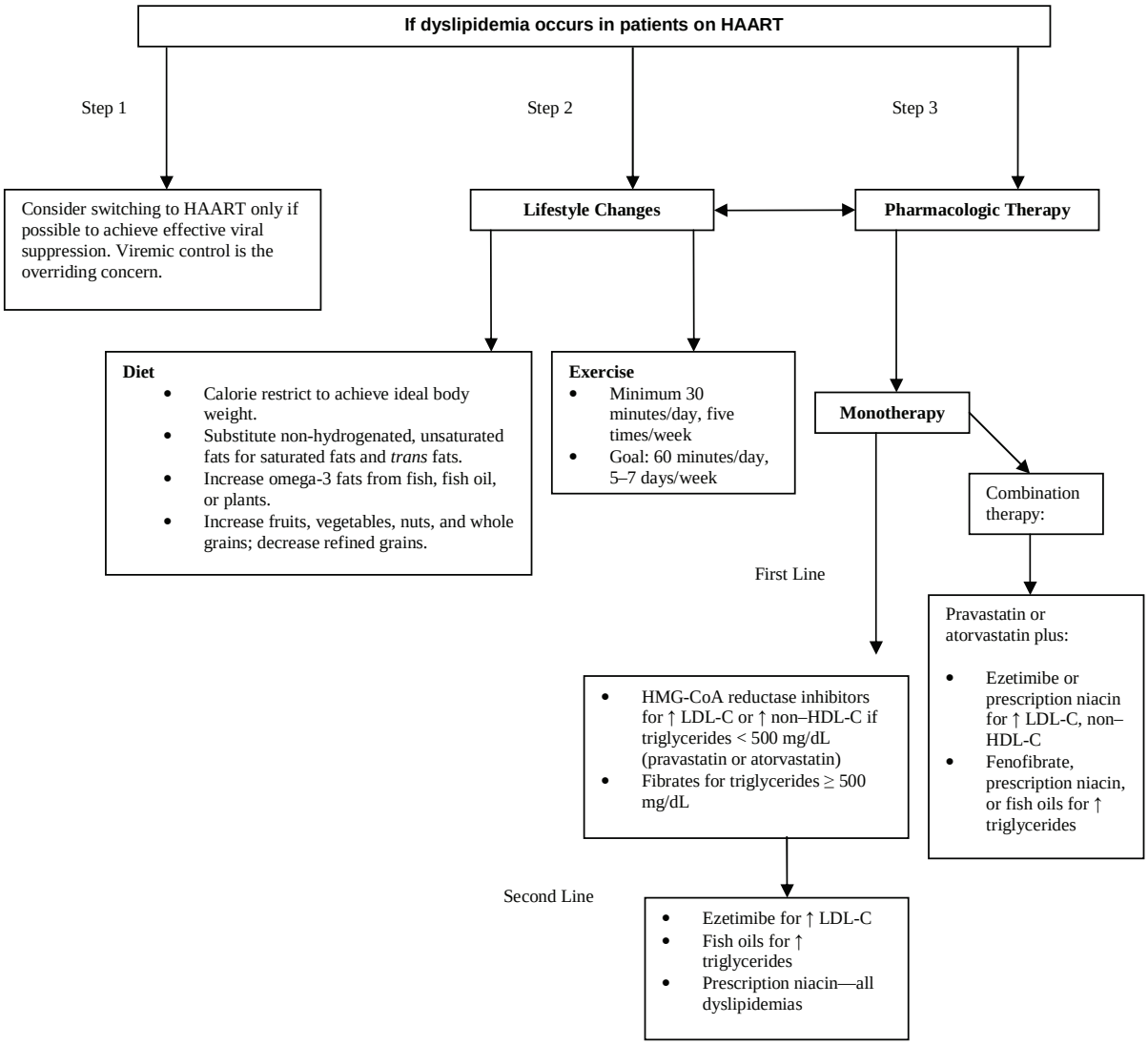

Figure 1-1. Treatment algorithm for HIV-associated dyslipidemia

Adapted with permission from Stein JH. Managing cardiovascular risk in patients with HIV infection. J Acquir Immune Defic Syndr 2005;38:115–22.
HAART = highly active anti-retroviral therapy; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C = low-density lipoprotein cholesterol.

placing patients at risk of CVD. Other metabolic adverse effects associated with anti-retroviral therapy include insulin resistance, lipoaccumulation, lipoatrophy, and lactic acidosis. Clinicians should be aware of a patient's CVD risk factors before starting anti-retroviral therapy; these include diabetes; hypertension; family history of CVD; age; male sex; race (African Americans and Hispanics account for a high proportion of patients with HIV infection); and smoking, which is also common in this patient population.

The heightened awareness of CVD in people infected with HIV is based on lipid abnormalities associated with anti-retroviral therapy, particularly PIs, that are well documented in numerous clinical trials. The magnitude of effect varies depending on the PI; ritonavir has the greatest propensity to increase lipids, even at low doses. Atazanavir, which is the only PI with a favorable lipid profile, loses some of this benefit when boosted with low-dose ritonavir. The only nucleoside reverse transcriptase inhibitor (NRTI) associated with lipid abnormalities is stavudine, which can cause hypertriglyceridemia. The NNRTIs are associated with considerably fewer lipid abnormalities than the PIs, although efavirenz occasionally causes hypertriglyceridemia. Compared with PIs and efavirenz, nevirapine has minimal effects on atherogenic lipids and increases high-density lipoprotein (HDL) cholesterol. The mechanisms responsible for lipid effects caused by anti-retroviral therapy have not been elucidated. Because drugs from three anti-retroviral classes can cause lipid abnormalities, the mechanisms are likely complex and probably involve multiple pathophysiologic processes.

Clinical studies have attempted to define the relationship between HIV infection, anti-retroviral therapy, and CVD. Most of these studies have major limitations because of the infrequent occurrence of cardiovascular end points and

relatively short exposure to HAART. A few studies have attempted to look at surrogate end points (i.e., carotid intima thickness and endothelial dysfunction or their changes) as evidence of atherosclerotic disease instead of cardiovascular events. Most of these studies, but not all, show patients receiving HAART, particularly PIs, to have increased subclinical atherosclerosis.

A few prospective longitudinal studies have shown that anti-retroviral therapy, specifically PI use, is associated with increased risk of myocardial infarction and cerebrovascular events. Two of the largest prospective studies of cohorts, with approximately 100,000 patient-years of combined follow-up, have shown that the incidence of myocardial infarction increased over time with HAART use. Even after adjustment for known cardiovascular risk factors, the use of PI-based HAART was still associated with increased risk of myocardial infarction. One interesting finding was that the larger of the two studies reported that the relative risk of myocardial infarction declined for each year of HAART. This finding is thought to be attributable to clinician awareness of HAART-associated dyslipidemia and to increasingly aggressive treatment with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors.

Treatment

Treatment, management, and evaluation of patients with HIV infection with dyslipidemia follow the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines, with a few exceptions caused by drug interactions (Figure 1-1). Whereas the NCEP ATP III guidelines are for the general population, guidelines were also published in 2003 to address the management of dyslipidemia in adults infected with HIV to help clinicians reduce CVD in this specific patient population. However, these guidelines lack the decades of evidence supporting the reduction in morbidity and mortality with lipid-lowering agents in adults who are not infected with HIV that led to the NCEP ATP III Guidelines. Recognition of dyslipidemia is reflected in the U.S. Department of Health and Human Services treatment guidelines for adults with HIV infection, which recommend a baseline fasting lipid profile for all patients with HIV infection before starting anti-retroviral therapy and within 3–6 months after initiating a new regimen. All patients with HIV infection should be evaluated for risk factors of coronary heart disease, which determine the appropriate low-density lipoprotein (LDL) cholesterol goal. Interventions that modify CVD risk factors, such as smoking cessation, weight loss, and exercise, should be offered. Smoking cessation is one of the most powerful interventions, other than the use of lipid-lowering drugs, in reducing cardiovascular risk.

For patients with hypercholesterolemia in addition to HIV infection, another approach to treating anti-retroviral–associated dyslipidemia is changing the offending agent. This switch strategy has been studied with atazanavir, nevirapine, and abacavir, and resulted in improved lipid profiles while maintaining viral suppression. The majority of these studies substituted one of these agents for a protease inhibitor; however, substitution with abacavir is associated with a higher risk of virologic failure if mutations in the HIV reverse transcriptase gene pre-exist. Few comparative studies have been performed between switch strategies and lipid-lowering agents; however, one study showed a greater lipid-lowering effect with the use of HMG-CoA reductase inhibitors. Ultimately, clinicians must weigh the risks of viral rebound and drug toxicity when switching anti-retroviral agents and compare them with the adverse effects from the addition of lipid-lowering drugs to the existing anti-retroviral regimen.

Therapeutic lifestyle changes should be implemented for 3 months, except in patients with severely elevated LDL cholesterol. Lifestyle changes include dietary and exercise interventions. In patients for whom the primary concern is the reduction of LDL cholesterol, HMG-CoA reductase inhibitors are the first choice. Clinicians should be aware that lovastatin, simvastatin, and rosuvastatin are contraindicated with PIs because of CYP 3A4 enzyme inhibition (primarily by ritonavir), resulting in significant increases in drug exposure (i.e., AUC) of these HMG-CoA reductase inhibitors; this can cause myopathy or rhabdomyolysis. Rosuvastatin is not extensively metabolized; however, when coadministered with lopinavir/ritonavir, an unexpected 5-fold increase in rosuvastatin AUC was observed. Based on these data, it is recommended that rosuvastatin be avoided with PIs. Atorvastatin is less dependent on CYP 3A4 for metabolism; however, when coadministered with lopinavir/ritonavir, atorvastatin AUC increased 6-fold. When the coadministration of atorvastatin and a PI is necessary, 10 mg of atorvastatin is recommended as a starting dose that is then titrated. Pravastatin is metabolized by multiple metabolic pathways, primarily glucuronidation, and is safe to administer with PIs. Caution should be used when pravastatin is coadministered with darunavir/ritonavir because of an unexpected drug interaction. Pharmacokinetic data have shown substantial interindividual variability in pravastatin exposure (up to a 5-fold increase in AUC). The recommendation is to start with the lowest dose of pravastatin and titrate to response if coadministered with darunavir/ritonavir. All HMG-CoA reductase inhibitors appear to be safe when used with NNRTIs; however, CYP 3A4 enzyme induction attributed to efavirenz and nevirapine decreases pravastatin and atorvastatin drug exposure based on decreased AUC. Ezetimibe has been studied in small numbers of patients with HIV infection and is safe and effective for adjunct therapy in patients who do not meet their LDL cholesterol goals.

Fibric acid derivatives are the drugs of choice when triglyceride concentrations are elevated. Guidelines for the treatment of dyslipidemia in patients with HIV infection recommend that fibrates be reserved for treatment when triglyceride concentrations are greater than 500 mg/dL. Both gemfibrozil and fenofibrate have been studied in patients with HIV infection and were found to be safe and effective. If mixed dyslipidemia is present, fenofibrate is considered safer than gemfibrozil when coadministration with an HMG-CoA reductase inhibitor is necessary. Fibric acid derivatives, particularly gemfibrozil, should be used cautiously with HMG-CoA reductase inhibitors because of increased risk of myalgia and myositis. If additional agents for hypertriglyceridemia are necessary, omega-3 fatty acids (fish oil) have been studied and are considered safe and effective. Patient intolerance, high frequency of dosing, and pill burden make fish oil less attractive than fibric acid derivatives.

Hepatitis C Coinfection

Morbidity and mortality caused by opportunistic infections in people with HIV infection have declined during the past decade, but morbidity and mortality from liver-related disease have increased. Coinfection with HCV is primarily responsible for this increase in liver-related disease. Liver disease progresses more rapidly and severely in patients coinfected with HIV and HCV compared with patients infected coinfected with HCV alone. Data from cohort studies show that for patients with HCV, progression to cirrhosis can occur within 6–10 years, whereas this progression for monoinfected patients takes an average of 20–30 years.

Because HIV and HCV share similar routes of transmission, coinfection is common, with estimated prevalence rates from 30% to 35%. Hepatitis C virus is a ribonucleic acid (RNA) virus that is different from HIV because it is not incorporated in the host cell genome. This means that HCV can be eradicated, resulting in a potentially curable disease. Eradication of HCV is critical to extend the survival benefits gained from HAART in patients with HIV infection. All patients with HIV infection should undergo screening for HCV antibody; if the HCV antibody is present, then these patients require further evaluation to determine if they are candidates for HCV treatment, including HCV genotype, HCV viral load, and liver transaminase concentrations.

Factors Affecting Treatment

Numerous factors can influence the success of HCV treatment in the coinfected patient population, such as HCV genotype, HCV RNA viral load, liver histology, HCV treatment duration, HCV therapeutic agents that are poorly tolerated, continued substance abuse, and mental illness. In addition, improving HCV treatment outcomes can depend on some HIV variables, such as higher CD4 T-lymphocyte count or low HIV viral load. The HCV genotype is particularly important because genotype 1, which constitutes 77% of all chronic HCV infection in the United States, and genotype 4 are more difficult to eradicate than genotypes 2 and 3. The value of a liver biopsy is still under debate, but it does provide valuable diagnostic and prognostic information. A liver biopsy is not mandatory for considering HCV treatment in coinfected patients. Noninvasive procedures such as new imaging techniques and serum biochemical markers can assess the degree of hepatic fibrosis. These tests may decrease the need for invasive biopsy procedures. The CD4 lymphocyte count is also important because patients with low counts (usually less than 200 cells/mL) have poor treatment response rates and are at risk of opportunistic infections in the short term because of lymphopenia from HCV treatment. Ideally, HCV treatment is best reserved for when CD4 lymphocyte counts are greater than 350 cells/mL. For patients with CD4 lymphocyte counts between 200 and 350 cells/mL, the decision to treat depends on the other predictors of response (HCV genotype, HCV viral load, or severity of liver disease) and the patient's clinical status. One clinical paradox is that most coinfected patients will be on HAART, which should result in increased CD4 lymphocytes. On one hand, this increase improves response to HCV therapy and diminishes the loss of CD4 lymphocytes that typically occurs during HCV treatment. On the other hand, coinfected patients are also at higher risk of liver toxicity from anti-retroviral agents. However, the benefits of treating HIV disease with anti-retroviral therapy clearly outweigh this risk in coinfected patients.

All PIs and NNRTIs can cause drug-induced hepatitis. Liver transaminases should be frequently monitored, especially in the first few months when these agents are initiated in coinfected patients. Liver enzyme elevations may occur by mechanisms other than direct injury from prescribed drugs, such as enhanced immune responses from HAART toward hepatic cells harboring HCV antigen, resulting in cellular destruction. As long as the patient remains asymptomatic and enzyme concentrations do not reach 10-fold above normal, anti-retroviral therapy should be continued. Elevated transaminases can be expected to return to baseline in most cases. Nevirapine and tipranavir have the greatest propensity to cause severe drug-induced liver disease in patients with HCV and are not recommended if other treatment alternatives are available. The NRTIs are also associated with increased toxicity when HCV treatment is necessary. Ribavirin increases the phosphorylation of the intracellular metabolites of didanosine, which has resulted in a higher incidence of pancreatitis, lactic acidosis, and decompensated liver disease; therefore, this combination of HCV treatment and NRTI is contraindicated. Enhanced mitochondrial damage is also observed with ribavirin and stavudine, which also should be avoided. Overlapping adverse effects, such as anemia and neutropenia, occur with ribavirin and zidovudine. Because ribavirin is critical for successful HCV treatment, zidovudine should be avoided because of the high incidence and severity of anemia.

Treatment

Successful treatment of patients with HCV is a challenge that is best served under the guidance of a multidisciplinary team. The combination of once-weekly pegylated interferon (180 mcg weekly) and daily ribavirin is the standard of care for patients coinfected with HCV. The dose of ribavirin is critical for HCV eradication and is based on weight and HCV genotype. Patients with genotype 1 or 4 should receive 1000 mg daily if they weigh less than 75 kg or 1200 mg daily if they weigh more than 75 kg; all other patients can receive 800 mg ribavirin daily. Complete blood counts must be frequently monitored because high-dose ribavirin can cause severe anemia, with hemoglobin and hematocrit abruptly falling within 1–4 weeks. Epoetin α (40,000 units weekly) and granulocyte colony-stimulating factor are commonly used to prevent ribavirin-associated bone marrow suppression.

Rates of sustained virologic response (defined as undetectable HCV viral load 6 months after completing HCV therapy) in coinfected patients range from 14% to 29% for genotype 1, which is approximately half the rate achieved for this genotype in patients without HIV infection. The reasons for outcome differences between the two groups are unclear, but treatment discontinuation is more common among coinfected patients. Pharmacists can help minimize treatment discontinuation by providing patient education about treatment, offering preemptive therapy to prevent side effects, emphasizing drug adherence (which

clearly results in improved treatment outcomes), providing pegylated interferon injection techniques, encouraging alcohol abstinence, and identifying drug-drug interactions.

Early virologic response is an important indicator of treatment success. Conversely, if patients fail to achieve at least a 2-log drop in HCV RNA by week 12 of therapy, the negative predictive value for sustained virologic response is extremely high. In these cases, HCV treatment should be stopped. This recommendation will spare drug-related side effects, cost, and resources and improve quality of life in patients who have no chance to eradicate HCV. Study data have shown that patients coinfected with HCV have higher baseline HCV RNA values than do HCV-monoinfected patients, which probably explains why they achieve undetectable HCV viremia at week 4 less commonly and, therefore, achieve sustained virologic response less often.

The optimal duration of treatment is not known, but typically, it is 48 weeks for coinfected patients regardless of HCV genotype. However, there are variables that can alter treatment duration; for instance, genotype 1 patients with high baseline HCV viral loads who do not have a rapid virologic response by week 4 should be considered to have their treatment extended to 72 weeks. Coinfected patients with genotype 2 or 3 with low baseline HCV viral loads who have a rapid virologic response by week 4 can be treated for 24 weeks. Regardless of treatment duration, drug adherence is critical for success, offering pharmacists multiple opportunities to encourage and assess adherence. A general rule regarding adherence for coinfected patients is that those who take more than 80% of pegylated interferon and ribavirin doses for at least 80% of the treatment duration are more likely to have successful treatment outcomes. Psychological and psychiatric adverse effects of pegylated interferon, such as depression, are major treatment-limiting factors. Clinicians who are trained to assess and treat depression can have a significant effect on the successful treatment of HCV in coinfected patients.

Finally, orthotopic liver transplantation is being performed for coinfected patients. The introduction of HAART and effective control of HIV infection dramatically improved the survival of liver transplant recipients and reduced the risk of opportunistic infections post-transplantation. Despite this, some drawbacks are the frequency of HCV recurrence after transplant and the significant drug interactions between anti-retroviral therapy and cyclosporine or tacrolimus, which require therapeutic drug monitoring. Factors independently associated with poor survival post-transplantation are intolerance to HAART, CD4 cell counts less than 200 cells/mm^3, and detectable HIV RNA.

Conclusion

Treatment of HIV infection continues to evolve and has become increasingly challenging. The focus has shifted from end-of-life care to management of HIV as a chronic disease. Polypharmacy is unavoidable for patients with HIV infection; therefore, clinicians need the necessary skills to understand pharmacokinetic and pharmacodynamic principles so that drug interactions can be managed or avoided altogether. Agents developed in the past few years have achieved treatment goals not previously seen in patients with multidrug-resistant HIV. The addition of new agents, with different mechanisms of action, makes the future of treating anti-retroviral–experienced patients very promising. Finally, although the benefits of HAART cannot be disputed, CVD caused by HAART-associated dyslipidemia and HCV coinfection need to be addressed to maintain survival benefits and ensure quality of life.

Annotated Bibliography

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   This Web site is an excellent up-to-date and comprehensive resource that allows clinicians to review published and unpublished data on drug interactions with HIV drugs. This site offers charts as a guide to interactions that may occur between different anti-retroviral agents and other drugs. Easy-to-use tables allow clinicians to choose drugs by pharmacological class and include drug interactions when multiple drugs are prescribed. The Web site is free and user-friendly, and it informs clinicians if drugs are contraindicated, if there is the potential for increases or decreases in drug concentrations, or if no known drug interactions exist. When data are available, clinicians can view the summary of the pharmacokinetic drug interaction in question. This site also allows clinicians to view drug interactions between anti-retroviral agents, which is particularly relevant when combinations of PIs and NNRTIs are being considered for a regimen. One limitation of this Web site is that not all pharmacologic drug classes are included, and not every drug from a particular therapeutic class is listed.

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   This Web site contains comprehensive, noncorporate, up-to-date information on HIV and AIDS treatment, prevention, and policy from the University of California, San Francisco. This site is free and provides excellent tables and charts to review dosage adjustment when anti-retroviral agents are coadministered with other anti-retroviral agents. The comprehensive database allows clinicians to search by anti-retroviral drug, interacting drug, or interacting drug class with easy-to-use pull-down lists. One advantage provided to clinicians are tables that explain the mechanism of the proposed drug interaction, potential adverse clinical effects, management strategies, suggested alternative agent(s), and appropriate published references. Charts and tables are arranged alphabetically to help the user quickly identify the drugs of interest. One limitation of this site is that clinicians need to read the tables closely because different doses of a specific drug are compared separately, which makes the tables somewhat difficult to interpret for clinicians who lack experience in the medical care of patients with HIV infection. Finally, this site is an excellent cross-reference to compare other drug interaction databases for clinical treatment decisions.

3. Nelson M, Arasteh K, Clotet B, Cooper DA, Henry K, Katlama C, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected

patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. J Acquir Immune Defic Syndr 2005;40:404–12.

The TORO studies (1 and 2) were randomized, open-label, controlled, Phase III studies in HIV treatment–experienced patients. Before the development of enfuvirtide (also known as T-20), virologic outcomes from treatment-experienced patients were poor, primarily because of the cross-resistance within each of the three classes of conventional anti-retroviral agents available. The TORO studies compared treatment with enfuvirtide (90 mg subcutaneously twice daily plus optimized background regimen of three to five anti-retroviral agents based on phenotypic and genotypic resistance tests) with optimized background regimen alone for 48 weeks in 1013 patients; TORO-1 was conducted in North America and Brazil, and TORO-2 was conducted in Europe and Australia. Patients had to have documented resistance to at least one drug from each anti-retroviral class and advanced HIV disease.

This article is the 48-week efficacy analysis (intent-to-treat) of data pooled from both studies. Ordinarily, this type of analysis is prone to errors; however, this analysis is justified because the two studies had similar designs, entry criteria, and protocol-specified analysis and because baseline demographics for each study population showed only minor differences. The analysis showed the low tolerability of enfuvirtide, which may be an issue in clinical practice. Local injection site reactions are the most commonly reported adverse effect (95% or greater), but only 3% discontinued treatment because of injection site reactions. This low discontinuation rate was likely because of a motivated study population who received additional support associated with their participation in a clinical trial. The results from this study changed the outlook for patients infected with multidrug-resistant virus. By week 48, a larger proportion of patients who received enfuvirtide than the control were in response categories of decrease in HIV viral load by greater than a 1.0-log change from baseline, less than 400 copies/mL, and less than 50 copies/mL (37%, 30%, and 18% in the enfuvirtide group compared with 17%, 12%, and 8% in the control group, respectively; $p<0.0001$ for all comparisons). Enfuvirtide-treated patients also responded better immunologically. Increases in CD4 lymphocytes from baseline were twice as great in the enfuvirtide group as in the control group. This study also found that patients with a lower baseline viral load, higher baseline CD4 count, less previous anti-retroviral experience, and more active drugs in the background regimen had the greatest magnitude of benefit of treatment, regardless of treatment group. The results and methodology of these two studies established how future studies for anti-retroviral treatment–experienced patients will be judged.

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This study, also referred to as the POWER 2 Study, evaluated the efficacy and safety of darunavir/ritonavir in four dosages in patients who had experienced virologic treatment failure with three or more classes of anti-retroviral agents. This article was the first significant publication for darunavir, a new PI with activity against multidrug-resistant HIV. This was a multicentered, randomized, controlled, Phase IIb study conducted in 278 patients. Before randomization, investigators selected an optimized background regimen and a PI regimen based on screening genotypic resistance data and treatment history. The optimized background regimen included at least two NRTIs, with or without enfuvirtide, and excluded NNRTIs. Patients were randomized to darunavir plus ritonavir arm(s) or the investigator-selected control PI arm. The results from this study confirmed darunavir/ritonavir 600/100 mg twice daily as the most effective dose for use in treatment-experienced patients. Patients in this study were heavily treatment experienced with a previous exposure to a median of 11 anti-retroviral agents and broad PI cross-resistance.

Results from this study are very impressive: 62% of patients who received darunavir/ritonavir had at least 1.0 log copies/mL HIV viral load reduction, and 39% had HIV viral load less than 50 copies/mL at week 24. In contrast, 14% and 7%, respectively, of the control PI arm achieved the same end points. These differences were statistically significant and clinically relevant. Increases in CD4 count were also higher for all darunavir/ritonavir dose groups (59–75 cells/mm^3) than for the comparator arm (12 cells/mm^3) ($p\leq0.005$). This finding is in contrast with the TORO trials, in which patients with extensive drug resistance treated with enfuvirtide plus NRTI and PI had improved viral load responses, but maximal viral suppression remained suboptimal. Results from the POWER 2 trial suggest that darunavir/ritonavir provides an excellent treatment option for treatment-experienced patients. The goals for treatment-experienced patients are being redefined; no longer are partial and transient HIV viral load reductions, with maintenance of immunologic function, acceptable goals for treatment-experienced patients. Instead, these data provide clinicians with more effective and durable strategies to achieve a goal of complete viral suppression. The major limitation of this study is the relatively short follow-up; results from 48 weeks are necessary to confirm the safety and efficacy data from this 24-week study. In addition, information is lacking regarding the patients who did not respond to darunavir/ritonavir.

5. Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomized controlled trial. Lancet 2007;369:1261–9.

This is the first significant efficacy study for integrase inhibitors, and it ushers in a new class of anti-retroviral therapy. This is a preplanned 24-week analysis of a continuing Phase II dose-ranging, double-blind, randomized, placebo-controlled study of treatment-experienced patients infected with multidrug-resistant HIV. The study objective was to assess the safety and efficacy of raltegravir compared with placebo. Both raltegravir and placebo arms received study treatment in combination with optimized background therapy. Human immunodeficiency virus integrase is a unique therapeutic target, and HIV integrase inhibitors would be expected to maintain activity against HIV resistant to the other classes of anti-retroviral agents. Similar in design to other treatment-experienced studies, this study required that patients have documented resistance to at least one NRTI, one NNRTI, and one PI. The optimized background regimen was selected based on screening resistance tests. The median number of previous anti-retroviral drugs for study participants was 12, and the median treatment duration was 9.9 years.

The preplanned 24-week analysis was impressive for patients receiving raltegravir. The efficacy at all doses was better than placebo when added to the optimized background regimen. The dosage chosen by the manufacturer to move

forward was 400 mg twice daily, which showed a viral load reduction of 1.87 log copies/mL from baseline compared with the 0.35-log reduction for the placebo arm. This study also achieved a viral load less than 400 copies/mL in 56% of participants and less than 50 copies/mL in 42% of participants compared with 16% and 13%, respectively, for placebo ($p<0.0001$). Anti-retroviral effects were observed as early as week 4 and were sustained through week 24 across all raltegravir groups. The superior efficacy of raltegravir was also evident whether or not enfuvirtide was part of the treatment regimen. Immunologic benefits were also observed: those patients receiving raltegravir had a median increase of 113 CD4 cells/mm^3 compared with 5 cells/mm^3 for placebo. Raltegravir at all doses had a safety profile similar to placebo; there were no dose-related toxicities. A limitation of this study is the short duration; 48-week follow-up data will be necessary to show that the potency and durability of raltegravir are maintained. Raltegravir resistance also was not reported in this analysis, but this information will be necessary for the clinical application of raltegravir. These data confirm that HIV integrase is a valid target for anti-retroviral therapy. The efficacy and tolerability of raltegravir suggest that this drug has the potential to become an important component of combination treatment regimens used to treat patients with multidrug-resistant virus who have limited treatment options and are not responding to current therapies.

6. Madruga JV, Cahn P, Grinsztejn B, Haubrich R, Lalezari J, Mills A, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomized, double-blind, placebo-controlled trial. Lancet 2007;370:29–38.

   This study is one of two studies (DUET-1 and -2) that were published in *Lancet* that evaluated two experimental drugs (etravirine and darunavir, which were not approved when the study began) that have activity in NNRTI- and PI-resistant viruses. This study is different from previous treatment-experienced patient studies because all patients received darunavir/ritonavir. Study participants also received optimized NRTIs (selected based on screening resistance test) and were randomized to receive etravirine or placebo and optional enfuvirtide. The rationale behind patients receiving darunavir/ritonavir was that the drug combination has shown antiviral efficacy in treatment-experienced patients. The use of darunavir/ritonavir ensured that all study participants received at least one active drug with demonstrated efficacy. The protocols were essentially identical between DUET-1 and -2; the only difference was the countries where the studies were conducted. Both studies reported similar findings and came to the same conclusions in different geographic populations.

   DUET-1 is a continuing, multinational, randomized, double-blind, placebo-controlled, phase III trial. The study assesses the safety, efficacy, and tolerability of etravirine in treatment-experienced patients. This article describes the protocol-specified week 24 primary analysis. Study participants had to have three or more primary PI mutations at screening and at least one NNRTI resistance–associated mutation. The primary end point was the proportion of patients achieving a confirmed viral load less than 50 copies/mL at week 24 (intention-to-treat analysis) and time to loss of virologic response. Secondary end points were the proportion of patients achieving a viral load less than 400 copies/mL, a change in viral load from baseline, a change in CD4 count from baseline, and safety and tolerability.

   The results from DUET-1 showed that the primary efficacy end point of a viral load less than 50 copies/mL was achieved by a significantly greater proportion of patients receiving etravirine than those receiving placebo. Additional benefits of etravirine over placebo were seen for secondary end points, including viral load less than 400 copies/mL, change in viral load from baseline, and change in CD4 cell count from baseline. Most treatment-emergent adverse effects were mild to moderate, and discontinuations were similar in both arms. The frequency and severity of hepatic, neuropsychiatric, and lipid-related adverse effects did not differ between etravirine and placebo arms. One particular adverse effect that was different between etravirine and placebo was rash (any type). Rash was documented in 20% of the etravirine group compared with 10% of the placebo group; however, cases were mild to moderate and infrequently led to discontinuations (2%).

   According to the authors, the virologic response observed in the etravirine group was better than in the placebo group, despite patients having at least one documented NNRTI resistance–associated mutation and an extensive treatment history. These data support etravirine as a new treatment option within the NNRTI class and confirm that it is probably effective even in the presence of NNRTI resistance. A few limitations must be acknowledged: one is that the PI component was fixed with darunavir/ritonavir. Etravirine cannot be administered with tipranavir; therefore, darunavir/ritonavir was considered the best PI option for this population with extensive PI resistance. In addition, quality-of-life measurements were not obtained for this study. The results are from 24-week data, and 48-week data will be necessary to determine if the benefits of etravirine are sustained. Finally, a detailed description between resistant genotype and treatment success is necessary to help gauge etravirine's prospects in individual patients.

7. Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). Guidelines for the use of anti-retroviral agents in HIV-1-infected adults and adolescents [monograph on the Internet]. Washington: U.S. Department of Health and Human Services. Available at *AIDSinfo.nih.gov*. Accessed July 7, 2007.

   This document provides the recommendations that clinicians consult for the management and treatment of people with HIV infection in the United States. This document is the standard of care for HIV treatment and usually is updated yearly. Include in this document are basic HIV patient evaluation, anti-retroviral treatment goals, time to initiate therapy, and choice of initial therapy. Also provided in this report are agents not to use and the rationale behind their avoidance, as well as limitations to treatment, including safety and efficacy. Recommendations for the treatment and management of anti-retroviral–experienced patients are discussed. Use of drug resistance testing in clinical practice is discussed. Also available in this document are considerations for anti-retroviral therapy in special populations, such as acute infection, adolescents, pregnancy, and hepatitis coinfection. Finally, this document has excellent tables on drug interactions and recommendations on when standard dosing of anti-retroviral agents requires modification. This is an excellent document for any clinician involved in HIV treatment and management.

8. Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT, et al. Guidelines for the evaluation and

management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving anti-retroviral therapy: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 2003;37:613–27.

These consensus recommendations from the HIV Medicine Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group help guide clinicians in the evaluation and treatment of lipid disorders in adults with HIV infection. This report reviews data on the incidence and prevalence of dyslipidemia and CVD in patients with HIV infection, pharmacokinetic profiles for lipid-lowering agents, and treatment trials of lipid-lowering agents in patients with HIV infection. Treatment-associated lipid disorders caused by PIs and NNRTIs are reviewed, as is the strategy for switching anti-retroviral therapies when one agent is considered the cause of hyperlipidemia. The majority of this report focuses on treatment and the clinical evaluation of the patient in terms of risk stratification according to NCEP ATP III guidelines published in 2001. This document should be used as a supplement to the NCEP ATP III guidelines to help guide clinicians when making treatment decisions for patients with HIV infection with dyslipidemia. Treatment of both hypercholesterolemia and hypertriglyceridemia is discussed, with particular attention to specific drug interactions between HMG-CoA reductase inhibitors and PIs and NNRTIs. This article is an excellent summary of applying the hyperlipidemia treatment guidelines for the general population to the HIV-infected patient population. Special considerations are the potential drug interactions with HIV drugs and the relatively short duration of safety and efficacy studies of lipid-lowering agents in patients with HIV infection.

9. Stein JH. Managing cardiovascular risk in patients with HIV-infection. J Acquir Immune Defic Syndr 2005;38:115–23.

This article reviews the cardiovascular risks in patients receiving HAART and discusses the implementation of the guidelines for the evaluation and management of dyslipidemia in adults with HIV infection receiving anti-retroviral therapy. The largest retrospective studies to date are reviewed and summarized regarding their main findings and limitations. The author also provides a critique of prospective studies, including two large studies evaluating cardiovascular risks of HIV infection. This article reviews the guidelines for the evaluation and management of dyslipidemia in adults with HIV infection receiving anti-retroviral therapy published by the Infectious Disease Society of America and Adult AIDS Clinical Trials Group and contains excellent treatment algorithms for clinicians to follow. Treatment recommendations include preferred agents, alternative therapies, and appropriate laboratory monitoring parameters. This article also ties in some of the more recent studies of patients with intermediate- and high-risk coronary heart disease without HIV infection and the implications for patients with HIV infection.

10. Grundy SM, Cleeman JI, Bairey Merz CN, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110:227–39.

The recommendations for treating patients with HIV infection and dyslipidemia are modeled after the 2001 NCEP ATP III guidelines; however, the recommendations for treating patients with HIV infection and dyslipidemia should still follow the updated NCEP ATP III guidelines discussed in this publication. The National Heart, Lung, and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association endorse this document. Since the publication of the NCEP ATP III evidence-based guidelines on cholesterol management in 2001, five major clinical trials of HMG-CoA reductase inhibitor therapy with clinical end points have been published. These trials address issues that other cholesterol-lowering agent trials had not examined. Results of these recent trials show that therapeutic lifestyle changes remain an essential component of clinical management. For patients who are considered very high risk (all patients with coronary heart disease or coronary heart disease risk equivalent), an LDL cholesterol less than 70 mg/dL is a therapeutic goal; for moderately high-risk patients (more than 2 risk factors, 10-year Framingham risk equation of 10% to 20%), LDL cholesterol less than 130 mg/dL is the desired goal. For patients at low risk (0 or 1 risk factor), LDL cholesterol less than 160 mg/dL is the goal. This document is the standard of care for patients with dyslipidemia and reviews results of recent trials and their implications for the current management of dyslipidemia.

11. Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV international panel. AIDS 2007;21:1073–89.

This document reviews data for the optimal management and treatment of chronic HCV infection in patients with HIV infection. The authors compare similarities and differences between the clinical management of people with HCV monoinfection and people coinfected with HCV and HIV with clinical data to support their recommendations. The authors have identified 11 areas in which further research and outcome data are necessary for the care of patients coinfected with HCV and HIV: Management of patients with persistently normal aminotransferases, when and how to assess liver fibrosis, predictors of response to HCV therapy in coinfected patients, optimal dosages of pegylated interferon and ribavirin, optimal duration of HCV therapy, treatment of non-responders or patients who relapse, care of patients with end-stage liver disease, treatment of acute HCV infection in patients with HIV infection, management of patients infected with multiple hepatitis viruses, interactions between HCV drugs and anti-retroviral drugs, and hepatotoxicity of anti-retroviral drugs. The authors state their recommendation(s) after discussing data for each of the listed topics in a short and concise manner. Limitations of this article are the failure to discuss HCV coinfection epidemiology data, the pathophysiology of HCV infection, and the barriers of adherence to pegylated interferon treatment.