ABSTRACT

Current treatment goals for patients with HIV are focused on reducing HIV-related morbidity, prolonging survival, improving quality of life, and preventing HIV transmission by maximally suppressing viral replication for as long as possible, while restoring or preserving immune function. To achieve these goals, clinicians must select a potent antiretroviral regimen from multiple drug classes, which preferably includes 3 active drugs against the major strains of HIV in a given patient. This article explores current treatment recommendations for treatment-naïve and treatment-experienced patients, from the Department of Health and Human Services’ Antiretroviral Guidelines for Adults and Adolescents. Also included are antiretroviral agents and combinations of agents that are not recommended due to lack of potency or safety concerns. For treatment-naïve patients, current “preferred” antiretroviral regimens consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs), combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI). Guideline-preferred antiretroviral agents for initial therapy include the NNRTI efavirenz; the PI-based regimens atazanavir + ritonavir, fosamprenavir + ritonavir, and lopinavir/ritonavir (coformulated); and the NRTIs abacavir/lamivudine (coformulated) and tenofovir/emtricitabine (coformulated). For treatment-experienced patients, strategies involved in managing virologic and immunologic failures, in addition to clinical progression, are discussed. (Adv Stud Pharm. 2008;5(4):97-104)

Although advances in antiretroviral therapy (ART) have transformed infection with HIV into a manageable chronic condition, complete viral eradication is still not possible. Even with prolonged suppression of plasma viremia, latently infected, resting CD4+ T cells persist. Researchers once speculated that early treatment of primary HIV infection may possibly prevent establishment of latent reservoirs, but subsequent studies examining very early initiation of highly active ART have not substantiated this theory. Therefore, treatment goals still focus on reducing HIV-related morbidity, prolonging survival, improving quality of life, and preventing HIV transmission by maximally suppressing viral replication for as long as possible, while restoring or preserving immune function.

To achieve these goals, clinicians must select a potent antiretroviral regimen from multiple drug classes, which preferably includes 3 active drugs that demonstrate activity against the major strains of HIV in a given patient. Clinicians must also be prepared to change regimens if maximum viral suppression is not achieved or maintained. One of the most important steps in achieving treatment goals is selecting an appropriate antiretroviral regimen for a treatment-naïve or treatment-experienced patient, which includes avoiding antiretroviral agents or combina-
tions of agents that lack potency or have safety concerns. This article focuses on current treatment recommendations from the Department of Health and Human Services’ (DHHS) Antiretroviral Guidelines for Adults and Adolescents, most recently updated on January 29, 2008, and available at http://aidsinfo.nih.gov/. Other factors involved in regimen success include optimizing patient adherence, avoiding deleterious drug interactions, and managing adverse events. These issues will be addressed in detail in the accompanying articles.

FIRST-LINE HAART (IN TREATMENT-NAÏVE PATIENTS)
In selecting an initial regimen for treatment-naïve patients with HIV, clinicians must not only consider genotypic or phenotypic drug resistance testing, but also patient comorbidities, the potential or desire for pregnancy, sex and pretreatment CD4 T-cell count (if considering nevirapine), and HLA-B*5701 testing (if considering abacavir). For treatment-naïve patients, current “preferred” antiretroviral regimens consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs), combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI; Table 1). Many of the preferred drugs are coformulated, which minimizes pill burden.

**NNRTI-BASED REGIMENS**
Non-NRTI–based regimens are among the simplest to take, particularly with the coformulated tablet containing tenofovir, emtricitabine, and efavirenz. This formulation allows a single pill to be taken once daily. Initial use of NNRTIs also delays the use of PIs.

### Table 1. Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment-Naïve Patients (Updated January 29, 2008)

<table>
<thead>
<tr>
<th>Preferred components</th>
<th>Column A (NNRTI or PI Options—in alphabetical order)</th>
<th>Column B (Dual-NRTI Options)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz* (AII)</td>
<td>atazanavir + ritonavir (AIII)</td>
<td>Preferred components</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir + ritonavir (2x/day) (AII)</td>
<td>(alphabetical order)</td>
</tr>
<tr>
<td></td>
<td>lopinavir/ritonavir (2x/day) (AII)</td>
<td>abacavir/lamivudine‡ (for patients who test</td>
</tr>
<tr>
<td></td>
<td>(coformulated)</td>
<td>negative for HLA-B*5701) (coformulated) (AII);</td>
</tr>
<tr>
<td></td>
<td>atazanavir (AII)</td>
<td>or tenofovir/emtricitabine‡ (coformulated) (AII)</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir (BII)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>atazanavir† (BII)</td>
<td>Alternative to preferred</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir + ritonavir (1x/day) (BII)</td>
<td>components (order of</td>
</tr>
<tr>
<td></td>
<td>lopinavir/ritonavir (1x/day) (BII) (coformulated)</td>
<td>preference)</td>
</tr>
<tr>
<td></td>
<td>saquinavir + ritonavir (BII)</td>
<td>zidovudine/lamivudine‡ (coformulated) (BII);</td>
</tr>
<tr>
<td>Preferred components</td>
<td>atazanavir + ritonavir (AII)</td>
<td>didanosine + (emtricitabine or lamivudine) (BII)</td>
</tr>
<tr>
<td>Alternative to</td>
<td>fosamprenavir + ritonavir (BII)</td>
<td></td>
</tr>
<tr>
<td>preferred components</td>
<td>atazanavir† (BII)</td>
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<td>lopinavir/ritonavir (1x/day) (BII) (coformulated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>saquinavir + ritonavir (BII)</td>
<td></td>
</tr>
</tbody>
</table>

*Efavirenz is not recommended for use in the first trimester of pregnancy or in sexually active women with childbearing potential who are not using effective contraception.

†The pivotal study that led to the recommendation of lopinavir/ritonavir as a preferred PI component was based on twice-daily dosing [Walmsley et al. N Engl J Med. 2002;346:2039-2046]. A smaller study has shown similar efficacy with once-daily dosing but also showed a higher incidence of moderate-to-severe diarrhea with the oncedaily regimen [16% vs 5%] [Johnson et al. J Acquir Immune Defic Syndr. 2006;43:153-160]. In addition, once-daily dosing may be insufficient for those with viral loads >100 000 copies/mL [Clumeck et al. 11th European AIDS Conference, 2007; Madrid. Abstract BPS 7/5].

‡Emtricitabine may be used in place of lamivudine and vice versa.

§Nevirapine should not be initiated in the following treatment-naïve patients: women with CD4 count >250 cells/mm³ or men with CD4 count >400 cells/mm³ because of increased risk for symptomatic hepatic events in these patients.

|| Azidovirine/lamivudine‡ (coformulated) (BII); or didanosine + (emtricitabine or lamivudine) (BII) |

and patient exposure to PI-associated adverse effects. However, a major disadvantage is the increasing prevalence of NNRTI-resistant strains (3%) versus PI-resistant strains (0.7%) in the treatment-naive population. Because of the K103R mutation, cross-resistance between NNRTIs is common. However, second-generation NNRTIs (such as etravirine) demonstrate in vitro activity against some NNRTI-resistant HIV. Because in general, drug-resistant HIV variants may be present in treatment-naive patients (especially those with HIV subtype B), resistance testing is now recommended before initiating therapy and should be used as a guide for selecting the optimal first regimen.

According to the DHHS guidelines, efavirenz is considered the “preferred” NNRTI, with nevirapine being an “alternative” option. Efavirenz-based regimens have been found to be virologically superior (either in potency or durability) to some PI-based regimens (ie, indinavir, lopinavir/ritonavir, and nelfinavir) and to triple-NRTI-based regimens. However, PI-based regimens can be associated with better CD4+ T-cell response and less drug resistance following virologic failure.

The decision to designate nevirapine as an “alternative” NNRTI in the DHHS guidelines was based largely on reports of serious hepatic events in treatment-naive patients, most of whom did not have identifiable underlying hepatic abnormalities. This complication has commonly occurred within the first few weeks of treatment, particularly in women with higher CD4+ T-cell counts (considered at highest risk). Nevirapine is, therefore, recommended only in treatment-naive women who have CD4+ T-cell counts of 250 cells/mm³ or lower or in men who have CD4+ T-cell counts of 400 cells/mm³ or lower.

**PI-BASED REGIMENS**

Factors, such as dosing frequency, food and fluid requirements, pill burden, drug interaction potential, baseline hepatic profile, and toxicity profile, must be considered when selecting a PI-based regimen. In general, PIs produce more gastrointestinal (GI) symptoms, lipid abnormalities, and a metabolic syndrome (ie, lipoatrophy, lipoaccumulation, and insulin resistance), which poses long-term cardiac and cosmetic concerns. Although initially these metabolic abnormalities and body shape changes were ascribed solely to PIs, NRTIs also appear to contribute to this complication (more information on adverse effects can be found in the article by Jennifer Cocohoba, PharmD).

Based on clinical trial efficacy, the barrier for virologic resistance, dosing convenience, and drug tolerability, the guidelines consider “preferred” PI-based regimens to include atazanavir + ritonavir, fosamprenavir + ritonavir, and lopinavir/ritonavir (coformulated). Ritonavir is used in each of these regimens to inhibit CYP3A and P-glycoprotein activity, thereby, increasing exposures of atazanavir, fosamprenavir, and lopinavir. Ritonavir-boosted atazanavir has the advantages of once-daily dosing and low pill burden. In studies comparing unboosted with boosted atazanavir, patients using boosted atazanavir had fewer virologic failures and less development of PI resistance mutations, but had greater lipid elevations. Other adverse effects associated with atazanavir + ritonavir include indirect hyperbilirubinemia (with or without jaundice or scleral icteris) and nephrolithiasis. If atazanavir is to be combined with tenofovir or efavirenz, it must be used in the ritonavir-boosted form to avoid deleterious drug interactions (more information on drug interactions can be found in Dr Cocohoba's article).

Fosamprenavir (prodrug of amprenavir) + ritonavir has comparable safety and efficacy to lopinavir/ritonavir, with approximately 70% of patients achieving HIV RNA lower than 400 copies/mL after 96 weeks of treatment. Both of these PI regimens are associated with metabolic side effects; however, more GI side effects are seen with lopinavir/ritonavir (approximately 16%) than with fosamprenavir/ritonavir (approximately 10%).

**DUAL-NRTI OPTIONS**

The guidelines have designated abacavir/lamivudine (coformulated) and tenofovir/emtricitabine (coformulated) as “preferred” NRTIs for use as part of initial combination therapy. After 48 weeks of therapy, patients taking abacavir + lamivudine have greater CD4+ T-cell counts than those taking zidovudine + lamivudine. This regimen can also be given as a once-daily fixed-dose formulation. Abacavir, however, is
associated with severe hypersensitivity reactions, which may be characterized by fever, rash, GI symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), generalized malaise, fatigue, dyspnea, cough, or pharyngitis. Therefore, screening for the major histocompatibility complex class I allele HLA-B*5701 is encouraged before the use of this NRTI. Abacavir must be avoided in those who test positive for HLA-B*5701. Patients who test negative for HLA-B*5701 are less likely to experience this reaction, but should still be counseled to watch for the symptoms of hypersensitivity.2

Tenofovir, a nucleotide analog with activity against HIV and hepatitis B virus, is available as part of a once-daily, fixed-dose combination with emtricitabine (in addition to the combination of tenofovir, emtricitabine, and efavirenz mentioned above). Treatment-naïve patients demonstrate superior virologic responses and less development of resistance with NRTI combinations that include tenofovir compared to zidovudine + lamivudine.17,18 The most concerning, although relatively rare, adverse effect associated with tenofovir is renal impairment, which is characterized by increased serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis. Patients with advanced disease and/or greater treatment experience, in addition to those with pre-existing renal impairment or on concomitant medications that are nephrotoxic, may be at higher risk for this complication.2

ANTIRETROVIRAL REGIMENS NOT RECOMMENDED

Certain antiretroviral regimens are not recommended in the current guidelines due to suboptimal efficacy, increased toxicity, or concerns over virologic antagonism.2 For example, NRTI monotherapy must not be used for treatment because of the rapid development of resistance. One possible exception is the use of zidovudine monotherapy in prevention of mother-to-child transmission in certain circumstances. Likewise, dual-nucleoside regimens are not recommended, because they are less effective in potency and durability than 3-drug regimens.19 With the exception of abacavir/lamivudine/zidovudine, and possibly zidovudine/lamivudine + tenofovir, triple-NRTI regimens also are not recommended for routine use due to suboptimal efficacy.2

ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED

Unacceptable toxicities are generally the rationale for recommending against the use of certain antiretroviral agents. For example, atazanavir and indinavir may cause grade 3 to 4 hyperbilirubinemia and jaundice, and the risk increases when they are used in combination.2 Combined use of didanosine and stavudine is associated with a high incidence of peripheral neuropathy, pancreatitis, and lactic acidosis, and has been implicated in the deaths of HIV-infected pregnant women.2 Combining 2 NNRTIs is not recommended, based on studies indicating an increased incidence of adverse events and treatment discontinuations with the combination of efavirenz + nevirapine.20 Emtricitabine + lamivudine have similar resistance profiles and are not recommended in combination.2 Finally, stavudine and zidovudine should not be used in combination due to demonstrated antagonism.2

MANAGING TREATMENT-EXPERIENCED PATIENTS

One of the greatest challenges in HIV care is finding therapies for treatment-experienced patients. Treatment failure can be manifested by virologic failure, immunologic failure, and/or clinical progression. Virologic failure is defined as the inability to achieve or maintain viral suppression lower than 50 copies/mL. Immunologic failure is the inability to achieve and maintain an adequate CD4+ T-cell response. Clinical progression is the occurrence or reoccurrence of HIV-related events. Many factors are involved in treatment failure and include higher pretreatment HIV RNA, lower pretreatment CD4+ T-cell counts, use of less potent regimens, medication nonadherence, suboptimal pharmacokinetics, and underlying drug resistance. The incidence of drug resistance is approximately 30% after 6 years of first-line treatment.21 In general, the success of second- and third-line therapy is diminished by the emergence of multiple resistance mutations to first-line therapy.2,22

General strategies for managing virologic failure include conducting resistance testing while a patient is still exposed to the failing regimen, designing a new regimen based on treatment history and the results of resistance testing, and selecting at least 2 new antiretroviral drugs for the subsequent regimen.2 Patients with virologic failure who receive at least 2 active drugs in their new regimen generally will have a more potent and prolonged virologic response than those taking regimens with fewer active drugs.2 Due to risks of developing rapid resistance, adding only 1 fully active drug to a new regimen is not recommended. Use of a completely new class of drugs (eg, integrase
inhibitor or chemokine receptor antagonist) along with ritonavir-boosted PIs is associated with a better virologic response. Other predictors of success include lower HIV RNA at the time of therapy change, higher CD4+ T-cell counts, and higher genotypic and/or phenotypic susceptibility scores. Also changing from nucleoside combinations that could result in immunologic nonresponse and CD4 cell count decline, such as tenofovir with didanosine, should be considered.

Strategies to manage immunologic failure have not been formally tested, but may include changing from an NNRTI-based regimen to a PI-based regimen (based on improved CD4+ T-cell responses in treatment-naive patients). Immune-based therapies (eg, interleukin-2) have increased CD4+ T-cell counts in some studies, but are not recommended because of the lack of definitive data, significant side effects, and the need for parenteral administration.

In managing clinical progression, clinicians must consider the possibility of immune reconstitution inflammatory syndrome (IRIS), which usually occurs within the first 3 months after starting ART. During this initial phase of therapy, patients with a responding immune system may develop an inflammatory response to indolent or residual opportunistic infections (eg, *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, and tuberculosis), which necessitates further evaluation and treatment. Potential mechanisms for the syndrome include a partial recovery of the immune system or exuberant host immunologic responses to antigenic stimuli. The overall incidence of IRIS is unknown, but it appears to be dependent on the population studied and its underlying burden of opportunistic infections. Anti-inflammatory therapy, rather than a change in the antiretroviral regimen, may be warranted, especially in those with adequate immunologic and virologic responses. Specific scenarios for managing treatment-experienced patients and special patient populations are included in Tables 2 and 3.

Newly approved agents in novel antiretroviral drug classes play a critical role in treatment-experienced patients. Maraviroc, for example, binds to the CCR5 receptor of the CD4+ T cell, inhibiting strains that use this coreceptor for cellular entry. Maraviroc in combination with optimized background therapy (based on treatment history and resistance testing) has demonstrated superior immunologic and virologic responses in treatment-experienced patients. However, because antiretroviral-experienced patients may carry CXCR4-tropic virus, patients must undergo screening for CCR5 tropism before starting this drug, which should be considered in patients who only have CCR5 virus-

### Table 2. Managing Treatment-Experienced Patients: Specific Clinical Scenarios

| Prior treatment with no resistance identified. | Consider the timing of the drug resistance test (eg, Was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (eg, in 2–4 wks) to determine whether a resistant viral strain emerges. Consider intensifying with 1 drug (eg, tenofovir) or pharmacokinetic enhancement (use of ritonavir if current PI is unboosted [eg, atazanavir or fosamprenavir]) in select cases. |
| Prior treatment and drug resistance. | The goals are to maximally suppress HIV RNA (eg, to <50 copies/mL) and to prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen soon after HIV RNA begins to increase. This will minimize the selection and accumulation of resistance mutations with continued viral replication. It is especially important to discontinue an NNRTI in a patient with ongoing viremia and evidence of NNRTI resistance to decrease the selection of additional NNRTI-resistance mutations. This will preserve the efficacy of second-generation NNRTIs. A new regimen should include at least 2, and preferably 3, fully active agents. |

**Extensive prior treatment and drug resistance and new regimen containing ≥2 fully active agents cannot be identified.** The goal is to maximally resuppress HIV RNA (eg, to <50 copies/mL). With the availability of new antiretroviral drugs (including new drug classes) this goal may be possible in many patients. In some cases, however, viral suppression can be difficult to achieve. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). Partial virologic suppression of HIV RNA >0.5 log_{10} copies/mL from baseline has been shown to correlate with clinical benefits; however, this must be balanced against the risk for accumulation of additional resistance mutations, which could potentially impact future treatment choices.

In this case, it may be reasonable to continue a patient on a partially effective regimen, rather than changing the regimen. Cohort studies suggest that continuing therapy decreases the risk of disease progression, even in the presence of viremia and the absence of CD4+ T-cell count increases. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA can be maintained at <10 000–20 000 copies/mL.

NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
HBV/HIV Coinfection

- If treatment is needed for HIV but not for HBV: The combination of tenofovir and emtricitabine or tenofovir and lamivudine should be used as the NRTI backbone of an antiretroviral regimen, which will have efficacy for both infections.
- If treatment for HBV is needed: Patients should be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against both viruses (as above). Management of HIV should be continued with a combination regimen to provide maximal suppression.
- Treating only HBV: In instances when HIV treatment is not an option or is not desirable, pegylated IFNα may be used for the treatment of HBV infection, because it does not lead to the emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10-mg dose; however, there is a theoretical risk for development of HIV resistance, because it has anti-HIV activity at higher doses and is related to tenofovir. Because of the risk for HIV resistance, the use of emtricitabine, lamivudine, tenofovir, or entecavir without a full combination antiretroviral regimen should be avoided.
- Need to discontinue emtricitabine, lamivudine, or tenofovir: Monitor clinical course with frequent liver function tests and consider the use of IFN, adefovir dipivoxil, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve.

HCV/HIV Coinfection

- Treatment of HCV is recommended according to standard guidelines, with preference for those with higher CD4 counts (>200 cells/mm^3). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible but may be complicated by pill burden, drug toxicities, and drug interactions.
- Differences in HCV therapy management in the presence of HIV coinfection include:
  - Ribavirin should not be given with didanosine due to the potential for drug-drug interactions leading to pancreatitis and lactic acidosis.
  - Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic; monitor serum transaminases.
  - Zidovudine combined with ribavirin is associated with higher rates of anemia; avoid this combination when possible.
  - Growth factors to manage IFN-associated neutropenia and ribavirin-associated anemia may be required.

Mycobacterium TB Disease or LTBI with HIV Coinfection

- Presence of active TB requires immediate initiation of treatment.
- The optimal timing of initiation of antiretroviral therapy in patients with active TB disease is not known. In antiretroviral-naïve patients, delay of antiretroviral therapy for 2–8 weeks after initiation of TB treatment may permit a better definition of causes of adverse drug reactions and may reduce the risk of IRIS (or a “paradoxical reaction”) once antiretroviral therapy is initiated, but delay may increase the risk of HIV-related complications and mortality, particularly in those with very low CD4 cell counts.
- Directed therapy of TB treatment is strongly recommended for HIV-infected patients with active TB disease.
- Despite pharmacokinetic drug interactions, rifampin should be included in regimens for patients receiving antiretroviral therapy, with dosage adjustment as necessary.
- Where available, rifabutin is the preferred rifamycin in patients with HIV who have active TB disease because of its lower risk of substantial interactions with antiretroviral therapy.
- Rifabutin-based regimens should be given ≥3 times weekly in HIV-infected patients with active disease and CD4 count <100 cells/mm^3; twice weekly is acceptable if CD4 count >100 cells/mm^3.
- Once-weekly rifapentine is not recommended in the treatment of active TB disease in patients with HIV.
- The optimal management of IRIS is unknown; TB treatment and antiretroviral therapy should be continued, along with use of nonsteroidal anti-inflammatory agents for milder cases and consideration of the use of high-dose corticosteroids for 1–4 weeks in severe cases, with the length of treatment and taper based on control of symptoms.
- Immune restoration as a result of antiretroviral therapy may be associated with conversion from a negative to a positive TST or IGRA in response to M TB-specific proteins; repeat TST or IGRA is recommended in previously TST-negative or IGRA-negative individuals after initiation of antiretroviral therapy when the CD4 cell count exceeds 200 cells/mm^3.
- HIV-infected individuals found to have LTBI, defined as ≥5-mm skin test induration or positive IGRA with no prior treatment for LTBI and after appropriate evaluation to rule out active TB disease and no prior treatment of LTBI, should commence treatment with isoniazid (with pyridoxine) for 6–9 months.

HBV = hepatitis B virus; HCV = hepatitis C virus; IFN = interferon; IGRA = IFNγ release assay; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent TB infection; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TB = tuberculosis; TST = tuberculin skin test.
es. CCR5 tropism is usually most prevalent during early stages of HIV. As HIV-1 disease progresses, CXCR4-utilizing viruses gradually increase in prevalence, frequently resulting in emergence of a dual-tropic virus (a virus that can use both CCR5 and CXCR4 coreceptors). Approximately 50% of treatment-experienced patients demonstrate the CCR5 virus only. Monogram Biosciences manufactures a molecular assay (Trofile; South San Francisco, CA) that is used to identify tropism of a patient’s HIV.

Raltegravir, the first integrase inhibitor to be approved by the US Food and Drug Administration, blocks strand transfer during integration of viral DNA into host cell DNA. Raltegravir-based regimens have demonstrated significantly better virologic responses at 24 weeks, compared with placebo, in treatment-experienced patients.

Etravirine, a new NNRTI, has demonstrated in vitro activity against efavirenz- and nevirapine-resistant strains. In studies of treatment-experienced patients, an etravirine-based regimen resulted in significantly better virologic responses over 24 weeks, compared with placebo. An etravirine regimen should include active agents in addition to 2 NRTIs, especially in patients with pretreatment NNRTI resistance.

Tiplanrivir and darunavir are newly approved PIs that have demonstrated activity against PI-resistant viruses and are indicated for patients who are highly treatment-experienced or who have HIV-1 strains resistant to multiple PIs. However, these PIs should be used only in regimens containing other active drugs, because accumulation of additional mutations in the presence of ongoing viremia may ultimately limit their antiretroviral activity.

CONCLUSIONS

The development of more potent and durable antiretroviral regimens, in addition to a better understanding of the relationship between HIV replication and immune function, has improved our ability to prevent the progression of HIV infection to AIDS. However, the optimal use of current therapies requires significant pharmacokinetic and pharmacodynamic knowledge. As antiretroviral options and combinations increase, the preferred list of regimens will continue to change. For pharmacists who help care for patients with HIV, it is critical to keep abreast of these developments by frequently reviewing treatment guidelines.

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