Treatment for Adult HIV Infection

2004 Recommendations of the International AIDS Society-USA Panel

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Context Substantial changes in the field of human immunodeficiency virus (HIV) treatment have occurred in the last 2 years, prompting revision of the guidelines for antiretroviral management of adults with established HIV infection.

Objective To update recommendations for physicians who provide HIV care regarding when to start antiretroviral therapy, what drugs to start with, when to change drug regimens, and what drug regimens to switch to after therapy fails.

Data Sources Evidence was identified and reviewed by a 16-member noncompensated panel of physicians with expertise in HIV-related basic science and clinical research, antiretroviral therapy, and HIV patient care. The panel was designed to have broad US and international representation for areas with adequate access to antiretroviral management.

Study Selection Evidence considered included published basic science, clinical research, and epidemiological data (identified by experts in the field or extracted through MEDLINE searches using terms relevant to antiretroviral therapy) and abstracts from HIV-oriented scientific conferences between July 2002 and May 2004.

Data Extraction Data were reviewed to identify any information that might change previous guidelines. Based on panel discussion, guidelines were drafted by a writing committee and discussed by the panel until consensus was reached.

Data Synthesis Four antiretroviral drugs recently have been made available and have broadened the options for initial and subsequent regimens. New data allow more definitive recommendations for specific drugs or regimens to include or avoid, particularly with regard to initial therapy. Recommendations are rated according to 7 evidence categories, ranging from I (data from prospective randomized clinical trials) to VII (expert opinion of the panel).

Conclusion Further insights into the roles of drug toxic effects, drug resistance, and pharmacological interactions have resulted in additional guidance for strategic approaches to antiretroviral management.

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THE INTERNATIONAL AIDS SOCIETY-USA panel last updated its guidelines for antiretroviral therapy in 2002.[1] Over the past 2 years, substantial new information has emerged influencing antiretroviral management. This includes the availability of several new drugs that increase therapeutic options (ie, atazanavir, emtricitabine, enfuvirtide, and fosamprenavir); the reporting of major randomized, multicenter trials that help define optimal initial regimens; an evolving understanding of the mechanisms and clinical significance of drug resistance, toxic effects, and interactions; and clinical trial results that address questions concerning strategic approaches to antiretroviral therapy (eg, structured treatment interruption).

These updated guidelines reflect the international perspectives of the panelists and are designed to serve as a tool for clinicians in countries where resources are sufficient to provide rela-

For editorial comment see p 266.

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Box. Strength of Evidence Rating Scale

I. Prospective clinical trials (ie, properly randomized controlled trials) or data from ancillary trials (pharmacological and drug interaction studies)
   A. Published
   B. Abstracts presented at scientific conferences
II. Cohort studies
III. Observational studies (including meta-analyses)
IV. Inferences from studies with similar drugs (or in similar settings)
V. Extrapolations from pathogenesis studies
VI. Uncontrolled studies (eg, pilot studies, exploratory studies, etc)
VII. Expert opinion (consensus of the panel in the absence of above evidence)

tively unrestricted choices of drugs and diagnostic monitoring tools; the World Health Organization has recently issued new guidelines for resource-limited settings.[2] As with previous editions, our updated guidelines center on 4 major questions: when to start antiretroviral therapy, what to start, when to change, and what to change to.

METHODS

The International AIDS Society-USA antiretroviral panel was convened in 1995 to develop treatment guidelines for adults infected with human immunodeficiency virus (HIV) in the developed world.[3] Panel members were selected by the International AIDS Society-USA and include physicians with expertise in basic science, clinical research, and HIV patient care and were not compensated.

The panel continually monitors medical and scientific advances and updates its recommendations when new data warrant a new report (approximately every 2 years). It reconvened in late 2003 to review new data that might change the 2002 recommendations.[1] Panel members identified and critically reviewed new data. A 5-member writing committee (P.G.Y., S.M.H., M.S.H., M.S.S., and M.S.) was appointed, which drafted the manuscript and made revisions based on subsequent panel meetings.

Published data and abstracts from selected scientific conferences (Conferences on Retroviruses and Opportunistic Infections; International AIDS Society Conference on HIV Pathogenesis and Treatment; Interscience Conferences on Antimicrobial Agents and Chemotherapy; Infectious Diseases Society of America Conferences, and others) were considered. Reports from between July 2002 and May 2004 were reviewed and data were extracted through MEDLINE searches using terms relevant to antiretroviral therapy). Recommendations are made for antiretroviral drugs approved in the United States as of mid 2004 for established HIV infection among adults.

Evidence strengths were rated according to type. We developed a rating scale for the evidence that was adapted from the US Preventive Services Task Force ratings and modified to be relevant for treatment of HIV (BOX).

Costs of specific medications and laboratory monitoring have not been considered in these recommendations. However, costs are important elements in therapeutic decision making. Recommendations herein were made by full panel consensus. In each section, relevant data appearing since the last edition of the guidelines[1] are presented, followed by the panel's recommendations with the evidence strength ratings indicated.

WHEN TO START ANTIRETROVIRAL THERAPY

Recent Data Addressing This Question

Randomized clinical trials have demonstrated a survival benefit with the use of antiretroviral therapy by patients with severe immunodeficiency.[1] For less severely compromised individuals (ie, asymptomatic individuals with CD4 cell counts >200/µL), there are no definitive data from prospective, randomized controlled studies to determine when antiretroviral therapy is associated with a survival benefit. In the absence of such data, the decision to initiate therapy should be made based on survival and disease progression information obtained from observational studies, the consequences of moderate degrees of immune deficiency, and the long-term safety of antiretroviral drugs.

Over the last 2 years, published results of antiretroviral-treated cohorts largely support previous recommendations. The largest study, which analyzed data from 12 574 patients, concluded that a prognosis could be best predicted by CD4 cell count and HIV RNA response after 6 months of treatment, independent of pretreatment values.[4,5] The HIV Outpatient Study analyzed data from 1464 patients from 10 clinics in the United States; after a median of 4 years of follow-up, patients with baseline CD4 cell counts between 200/µL and 350/µL who started antiretroviral therapy had lower mortality rates than those who waited until their CD4 cell count was below 200/µL.[6] Another study reported outcomes of 1173 patients initiating therapy after July 1, 1996, and receiving therapy for at least 90 days.[7] Those who initiated therapy with a CD4 cell count below 200/µL had a higher risk of disease progression even if a durable virological suppression was achieved. In a cohort of 1422 treatment-naive patients in Canada (median follow-up, 40 months), CD4 cell count was the best predictor of survival, but a baseline HIV RNA level higher than 100 000 copies/mL was independently associated with death.[8] This group also studied a cohort with pretreatment CD4 cell counts between 200/µL and 350/µL.[9] After a median follow-up of more than 3 years, medication adherence (as estimated by prescription refills) was the critical determinant of survival. In a study performed in 1132 women infected with HIV (median follow up, 3.9 years), posttherapy CD4 cell counts

(<200/μL vs >350/μL) and HIV RNA level (>10 000 copies/mL vs <80 copies/mL) predicted death and new AIDS-defining illness. Pretherapy values were not predictive of clinical outcomes if adjusted for values attained after therapy initiation.[10]

Several potentially life-threatening conditions that may negatively affect survival, including tuberculosis and lymphomas, are common in individuals with moderately advanced immunodeficiency (ie, CD4 cell count between 200/μL and 350/μL).[11,12] The use of antiretroviral therapy may decrease the incidence of tuberculosis, and perhaps some other conditions, and thereby influence survival.

Arguing against earlier introduction of antiretroviral therapy are concerns over the long-term safety of therapy; toxic effects; potential cardiovascular consequences; and the negative impact of fat maldistribution on quality of life. In contrast, recent data have demonstrated long-term safety of some drugs and regimens over others.[13,14] Some treatment complications (eg, lipoatrophy)[15] may be more frequent and severe when therapy is initiated at lower CD4 cell counts.

Taken together, data from observational cohorts indicating that antiretroviral therapy may decrease the incidence of potentially life-threatening conditions, long-term safety data on some regimens, and the availability of newer drugs that are safer and easier to take, argue for initiation of therapy before HIV-related disease becomes clinically manifest whenever possible. However, the fact that a high proportion of patients first present to care with advanced HIV disease and CD4 cell counts below 200/μL[16] emphasizes the need for more aggressive voluntary counseling and testing initiatives to identify patients at earlier stages of disease.[17]

Recommendations

Therapy is recommended for all patients with symptomatic HIV disease (evidence strength rating, IA; TABLE 1).[1] The treatment of potentially life-threatening opportunistic diseases, or conditions that require drugs that are difficult to coadminister with antiretroviral drugs (eg, tuberculosis or hepatitis C virus coinfection) or can lead to an immune reconstitution syndrome following the initial CD4 cell count increase, may take precedence over immediate initiation of antiretroviral therapy (evidence strength rating, IV). There are sufficient data to continue to recommend antiretroviral treatment initiation before CD4 cell counts reach 200/μL (evidence strength rating, II).[1] Initiation of therapy in patients with CD4 cell counts below 350/μL but above 200/μL needs to be individualized (evidence strength rating, II). For example, low HIV RNA level, stable CD4 cell count (or one that is declining slowly; eg, a loss of fewer than 50/μL per year), and patient reluctance to start therapy, may be reasons to defer therapy. Conversely, plasma HIV RNA levels above 100 000 copies/mL or a CD4 cell count loss of more than 100/μL per year may be reasons to initiate therapy. Initiation of therapy is generally not recommended for patients with CD4 cell counts between 350/μL and 500/μL, but it may be considered in cases with high plasma viral load or a rapid decline in CD4 cell count (evidence strength rating, II).

Table 1. Recommendations for Initiating Therapy in Treatment-Naive Individuals*

Disease Stage	Recommendation	Evidence Rating†
Symptomatic HIV disease	Antiretroviral treatment	IA
Asymptomatic HIV disease		
≤200 CD4 cells/μL	Antiretroviral treatment	II
>200 CD4 cells/μL but ≤350 CD4 cells/μL	Antiretroviral treatment should be considered‡	II
>350 CD4 cells/μL but ≤500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention§	II
>500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention	II

Abbreviation: HIV, human immunodeficiency virus.
*Excludes pregnant women with specific regard to prevention of HIV transmission to the infant.
†See Box for explanation of evidence ratings.
‡The closer to 200 CD4 cells/μL, the stronger the recommendation for treatment, particularly if the plasma viral load is high (>50 000-100 000 copies/mL) or if the CD4 cell count is declining rapidly (>100/μL per year).
§Consider treatment for patients with high plasma viral load or with rapid decline of CD4 cell count.

CHOICE OF INITIAL REGIMEN

Recent Data Addressing This Question

Within the past few years it has become clear that not all antiretroviral regimens are equivalent in potency or toxicity. Initial regimens must still be individualized,[1] and the choice is influenced by several factors including comorbid conditions, the patient's readiness to start therapy, and concomitant medications, but it is now possible to say that certain initial regimens are generally preferable to others based on data from controlled clinical trials. Since publication of the last article, evaluations of regimens that contain nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and triple-nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs), and dual-NRTI backbones have been reported. Furthermore, several more convenient and tolerable formulations and fixed-dose combinations of drugs have become available. These formulations should improve adherence and ultimately improve therapeutic success, but there are no data from clinical trials demonstrating improved outcome for most of these formulations.

NNRTI-Based Regimens and Dual NRTI Backbones

The AIDS Clinical Trial Group 384 study was a multicenter, randomized, partially double-blind trial in 980 participants enrolled in the United States and Italy (median follow up, 2.3 years).[13,14] A factorial design was used to compare regimens and a composite end point was used that included viral suppression and toxicity. The combination of zidovudine, lamivudine, and efavirenz was superior to the other

3-drug regimens studied (zidovudine, lamivudine, and nelfinavir; stavudine, didanosine, and nelfinavir; or stavudine, didanosine, and efavirenz)[13] and was similar to a 4-drug regimen consisting of nelfinavir and efavirenz with either zidovudine and lamivudine or stavudine and didanosine. There was no statistically significant difference in the duration of successful treatment between a single 4-drug regimen and 2 consecutive 3-drug regimens.[14] The 4-drug regimen was associated with a longer time to first regimen failure than the 3-drug regimens except for the combination of zidovudine, lamivudine, and efavirenz.

The NRTIs used in the 3- or 4-drug combinations influenced toxicity risk, with higher incidences of peripheral neuropathy, pancreatitis, and hepatic enzyme abnormalities in regimens containing stavudine and didanosine.[14] From this and earlier studies,[18] it is clear that a combination of zidovudine, lamivudine, and efavirenz is a particularly useful initial regimen. However, the risk of virological resistance to lamivudine and efavirenz is high if strict adherence to the regimen cannot be maintained, given the low barrier to resistance with these 2 drugs.[19,20]

In the CNA30024 study, a combination consisting of abacavir, lamivudine, and efavirenz was similar (noninferior) to a combination consisting of zidovudine, lamivudine, and efavirenz in 649 patients receiving treatment for 48 weeks (HIV RNA level <50 copies/mL in 70% and 69% of patients, respectively).[21] There was a larger CD4 cell count increase with abacavir than with zidovudine. However, hypersensitivity was reported in 9% of patients taking abacavir. Gilead 903 was a trial comparing stavudine and tenofovir, each combined with lamivudine and efavirenz in 600 participants.[22] Levels of HIV RNA suppression (<50 copies/mL) and increases in CD4 cell count were similar at 96 weeks. However, stavudine-treated participants had a greater risk of elevated fasting triglyceride and cholesterol levels and peripheral neuropathy over 96 weeks.

Interim results from the FTC-301 double-blind, placebo-controlled study showed that emtricitabine, a recently approved NRTI, provided better viral suppression than stavudine when each was combined with didanosine and efavirenz in treatment-naive patients (TABLE 2).[23] This led to a decision by an independent data and safety monitoring board to discontinue the study after 24 weeks. The proportion of patients with persistent HIV RNA suppression below 50 copies/mL through week 60 was 76% for the emtricitabine group and 54% for the stavudine group (log-rank, $P<.001$). Patients receiving stavudine were more likely to experience treatment-limiting toxic effects and to prematurely discontinue therapy. Of note, there are fewer efficacy and safety data for emtricitabine (which is similar to lamivudine) or tenofovir than for the other NRTIs.

The NNRTI nevirapine has been evaluated in combination with 2 NRTIs. In 2 relatively small controlled trials, nevirapine was compared with a protease inhibitor (indinavir in ATLANTIC[24] and nelfinavir in COMBINE[25]). In the ATLANTIC study, 55% of participants in the nevirapine group and 44% in the indinavir group had HIV RNA levels below 50 copies/mL at 98 weeks.[24] In the COMBINE study, 75% of nevirapine and 60% of nelfinavir participants had HIV RNA levels below 200 copies/mL at 12 months ($P=.06$).[25]

In the 2NN study, nevirapine and efavirenz were compared when each was combined with stavudine and lamivudine.[26] A total of 1216 participants were randomized to receive 400 mg/d of nevirapine; 200 mg of nevirapine twice daily; 600 mg/d of efavirenz; or 400 mg/d of nevirapine and 600 mg/d of efavirenz. At 48 weeks, treatment failed in 43.6% of participants in the group receiving nevirapine once daily, 43.7% of the twice daily nevirapine group, 37.8% of efavirenz group, and 53.1% of the nevirapine and efavirenz group. A difference between the nevirapine and efavirenz groups of 10% at 48 weeks was prespecified to be clinically meaningful. This magnitude of difference cannot be ruled out based on the upper bound of the 95% confidence interval (CI). The mean proportions of patients reaching an HIV RNA level below 50 copies/mL at 48 weeks were not different among groups (70.0% for once daily nevirapine, 65.4% for twice daily nevirapine, 70.0% for efavirenz, and 62.7% for the combination of nevirapine and efavirenz). Adverse events or HIV progression caused treatment discontinuation in 21.5% receiving nevirapine twice daily, 15.8% receiving efavirenz ($P=.04$), and 30.1% receiving nevirapine and efavirenz. More participants in the nevirapine groups than in the efavirenz group had grade 3 or 4 clinical hepatotoxicity, but the differences were statistically significant only in the twice daily nevirapine group (2.1% for twice daily nevirapine, 1.4% for once daily nevirapine, and 0.3% for efavirenz). Compared with efavirenz (4.5%), more patients taking nevirapine either twice daily (8.3%) or once daily (13.6%) had grade 3 or 4 elevations in liver function tests. Two deaths were attributed to nevirapine, one due to hepatitis and another to Stevens-Johnson syndrome. Women (including pregnant women) who are taking nevirapine-containing regimens and who have CD4 cell counts greater than 250/μL are at a 12-fold greater risk of hepatotoxicity.[27] The highest risk for potentially fatal hepatotoxicity is in the first 6 weeks of therapy.[27] These results underline the importance of careful monitoring of liver enzyme tests in patients taking nevirapine (TABLE 3).

Protease Inhibitor-Based Regimens

In a double-blind, placebo-controlled trial enrolling 653 adults, lopinavir/ritonavir and nelfinavir were compared when each was used in combination with stavudine and lamivudine.[28] The primary end points were HIV RNA level of less than 400 copies/mL at week 24 and time to loss of virological response through week 48. All comparisons favored lopinavir/ritonavir. At week 48, 75% of participants in the group taking lopinavir/ritonavir had an HIV RNA level of less than 400

Table 2. Selected Randomized Studies of Emtricitabine and Atazanavir

Study Code, Drug, and No. of Patients	CD4 Cells/μL	Log_{10} HIV RNA copies/mL	Follow-up, wk	End Point		
				Percentage <50 HIV RNA copies/mL	Increase in CD4 Cells/μL	Important Safety Results*
FTC-301; emtricitabine[43] (N = 571 treatment naive)	288	4.9	24			
200 mg/d of emtricitabine plus didanosine and efavirenz				81	152	Discontinued due to adverse effects, 6.7%
40 mg of stavudine twice daily plus didanosine and efavirenz				70	117	Discontinued due to adverse effects, 13.9%
AI424-008; atazanavir[30] (N = 467 treatment naive)	295	4.73	48			
400 mg/d of atazanavir plus stavudine and lamivudine				35	234	Jaundice, 11%; diarrhea, 20%; total bilirubin, 41%†; total cholesterol, +5%; LDL cholesterol, +5%; triglycerides, +7%
600 mg/d of atazanavir plus stavudine and lamivudine				36	243	Jaundice, 20%; diarrhea, 15%; total bilirubin, 58%†; total cholesterol, +6%; LDL cholesterol, +7%; triglycerides, +8%
1250 mg of nelfinavir twice daily plus stavudine and lamivudine				34	211	Jaundice, 0%; diarrhea, 56%; total bilirubin, 4%†; total cholesterol, +25%; LDL cholesterol, +23%; triglycerides, +50%
AI424-034; atazanavir[31] (N = 810 treatment naive)			48			
Atazanavir plus zidovudine and lamivudine	286	4.87		32	176	Any clinical event, 41%‡; jaundice, 6%; rash, 6%; total bilirubin, 33%; LDL cholesterol, +1%; HDL cholesterol, +13%
Efavirenz plus zidovudine and lamivudine	280	4.91		37	160	Any clinical event, 45%‡; jaundice, 0%; rash, 10%; total bilirubin, <1%; LDL cholesterol, +18%; HDL cholesterol, +24%
AI424-043; atazanavir[71] (N = 300 treatment experienced)			24			
400 mg/d of atazanavir plus 2 NRTIs	288	4.18		–1.67§	94	Total cholesterol, –2%; LDL cholesterol, –6%; triglycerides, –2%
400 mg of lopinavir plus 100 mg of ritonavir twice daily plus 2 NRTIs	261	4.14		–2.11§	121	Total cholesterol, +17%; LDL cholesterol, +5%; triglycerides, +55%
AI424-045; atazanavir[32] (N = 358 treatment experienced)			48			
300 mg/d of atazanavir plus 100 mg/d of ritonavir or a combination of atazanavir and saquinavir plus tenofovir and 1 NRTI	317	4.44		38	110	Total cholesterol, –8%; LDL cholesterol, –10%; HDL cholesterol, –7%; triglycerides, –4%
400 mg/d of atazanavir plus 1200 mg/d of saquinavir or a combination of lopinavir and ritonavir plus tenofovir and 1 NRTI	283	4.47		46	121	Total cholesterol, +6%; LDL cholesterol, +1%; HDL cholesterol, +2%; triglycerides, +30%
400 mg of atazanavir plus 100 mg of ritonavir twice daily plus tenofovir and 1 NRTI	286	4.42		26	72	Total cholesterol, –4%; LDL cholesterol, –3%; HDL cholesterol, +4%; triglycerides, –14%

Abbreviations: HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor.
*Clinical events (jaundice, rash, diarrhea) and laboratory events (total bilirubin elevations) expressed as percentage of patients experiencing the event; lipid results are expressed as percentage change (plus sign, increase; minus sign, decrease) from baseline.
†Grade 3 or higher.
‡Clinical events higher than grade 2.
§Values are log changes.

Table 3. Selected Randomized Studies of Enfuvirtide and Fosamprenavir

Study Code, Drug, and No. of Patients	CD4 Cells/μL	Log_{10} HIV RNA copies/mL	Follow-up, wk	End Point		Important Safety Results*
				Percentage <50 HIV RNA copies/mL	Increase in CD4 Cells/μL	
TORO1; enfuvirtide[61] (N = 501 treatment experienced)			24			TORO1 and TORO2 pooled data: 3.7% discontinued enfuvirtide for injection site reactions; hypersensitivity, 1%; pneumonia, 5.6% in enfuvirtide group and 0.6% in optimized background group
Optimized background of 3-5 antiretrovirals (history plus resistance testing)†	87	5.2		7.3	32	
Optimized background plus 90 mg of enfuvirtide subcutaneously twice daily	75	5.2		19.6	76	
TORO2; enfuvirtide[60] (N = 512 treatment experienced)			24			TORO1 and TORO2 pooled data: 3.7% discontinued enfuvirtide for injection site reactions; hypersensitivity, 1%; pneumonia, 5.6% in enfuvirtide group and 0.6% in optimized background group
Optimized background of 3-5 antiretrovirals (history plus resistance testing)‡	101	5.1		5.3	38	
Optimized background plus 90 mg of enfuvirtide subcutaneously twice daily	98	5.1		12.2	65	
SOLO; fosamprenavir[41] (N = 660 treatment naive)			48			
1400 mg/d of fosamprenavir plus 200 mg/d of ritonavir plus abacavir and lamivudine	166§	4.78		56	396	Diarrhea, 9%
1250 mg of nelfinavir twice daily plus abacavir and lamivudine	177‖	4.83		52	385	Diarrhea, 16%
NEAT; fosamprenavir[72] (N = 251 treatment naive)¶			48			
1400 mg of fosamprenavir twice daily plus abacavir plus lamivudine	211	4.82		55	201	Diarrhea, 5%
1250 mg of nelfinavir twice daily plus abacavir plus lamivudine	213	4.85		41	216	Diarrhea, 18%
CONTEXT; fosamprenavir[63]† (N = 320 treatment experienced)	263	4.14	24			
700 mg of fosamprenavir plus 100 mg of ritonavir twice daily plus 2 optimized NRTIs				−1.48#	62	Clinical events ≥ grade 2, 35%; total cholesterol, 0%; triglycerides, +8%
1400 mg of fosamprenavir plus 200 mg of ritonavir once daily plus 2 optimized NRTIs				−1.46#	72	Clinical events ≥ grade 2, 19%; total cholesterol, 0%; triglycerides, +4%
400 mg of lopinavir plus 100 mg of ritonavir twice daily plus 2 optimized NRTIs				−1.63#	63	Clinical events ≥ grade 2, 34%; total cholesterol, 0%; triglycerides, +4%

Abbreviations: HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor.
*Clinical events are expressed as percentage of patients with event. Lipid results are expressed as percentage change (plus sign, increase) from baseline. Total cholesterol and triglyceride events are of grade 3 or higher.
†A total of 336 patients received 2 or fewer active drugs in optimized background (based on genotype).
‡A total of 385 patients received 2 or fewer active drugs in optimized background (based on genotype).
§Nineteen percent of the patients had a CD4 cell count of less than 50/μL.
‖Twenty-one percent of the patients had a CD4 cell count of less than 50/μL.
¶Eighteen percent of the patients had a CD4 cell count of less than 50/μL.
#Values are log changes.

copies/mL compared with 63% in the nelfinavir group; similar differences were observed when the cutoff for HIV RNA level was below 50 copies/mL. Average triglyceride increases were greater in the group receiving lopinavir/ritonavir (125 mg/dL increase) than in the group receiving nelfinavir (47 mg/dL increase) ($P<.001$). Protease inhibitor–resistance mutations were demonstrated in 33% of participants in whom nelfinavir was failing and in none of 37 patients in whom lopinavir/ritonavir was failing.

A twice daily regimen including 1000 mg of saquinavir and 100 mg of ritonavir was compared with 800 mg of indinavir and 100 mg of ritonavir twice daily in 306 participants (only one third of whom were treatment naive).[29] Virological results at 48 weeks were comparable ($P=.84$), but when treatment changes were considered failures, the regimen with saquinavir and ritonavir appeared better ($P=.01$) and was associated with fewer lipid level increases.

Atazanavir is a recently approved once daily protease inhibitor. Initial comparative studies have shown somewhat contradictory results (Table 2). In the AI424-008 study, atazanavir and nelfinavir had similar responses when each was combined with 2 NRTIs.[30] In the AI424-034 study,[31] atazanavir was compared with efavirenz, each in combination with zidovudine and lamivudine. Virological results at week 48 were comparable, although the responses in the efavirenz group were below those seen in previous trials (eg, 37% receiving efavirenz achieved a level of HIV RNA <50 copies/mL vs >70% in previous studies). The rates of detected plasma HIV RNA may have been overestimated in AI424-034 because of technical problems with sample processing. In both studies, lack of lipid level changes favored atazanavir.

Evaluations of atazanavir and low-dose ritonavir in initial regimens also are under way. A preliminary study (AI424-045) in antiretroviral-experienced patients (Table 2) suggests that the combination of atazanavir and ritonavir has similar antiretroviral activity and fewer hyperlipidemic effects than other regimens containing ritonavir-boosted protease inhibitors.[32]

Few studies have compared the regimens containing a boosted protease inhibitor with regimens containing efavirenz. The FOCUS trial compared a regimen including 1600 mg of saquinavir and 100 mg of ritonavir with one including efavirenz in 152 individuals.[33] The efavirenz group had better HIV RNA suppression (71% reached a level of <50 copies/mL compared with 51% in the saquinavir and ritonavir group) at 48 weeks. The CLASS study[34] compared the following combinations: amprenavir and ritonavir with abacavir and lamivudine; efavirenz and abacavir and lamivudine; and stavudine with abacavir and lamivudine. Preliminary results at 48 weeks showed HIV RNA suppression (<50 copies/mL) superiority in the the efavirenz group (76%) compared with the amprenavir and ritonavir group (59%) or the stavudine group (62%).

Triple NRTI-Based Regimens

AIDS Clinical Trial Group 5095 is an 1147-patient, ongoing, placebo-controlled, double-blind study designed to compare combinations of zidovudine, lamivudine, and abacavir; zidovudine, lamivudine, and efavirenz; and zidovudine, lamivudine, abacavir, and efavirenz. A scheduled data and safety monitoring board review found differences between the 3-NRTI group and each of the other groups that crossed prespecified stopping boundaries; the 3-NRTI group was discontinued.[35] After a median follow-up of 32 weeks, treatment failed in 21% of the 3-NRTI group and in 11% of the pooled efavirenz groups (regardless of pretreatment HIV RNA level of >100 000 copies/mL or HIV RNA level of <100 000 copies/mL).

The CLASS and ATLANTIC studies[24,34] also suggest that stavudine-based triple-NRTI regimens are less effective than other regimens. In ATLANTIC, stavudine and didanosine were combined with nelfinavir, nevirapine, or lamivudine. Viral load response in the 3-NRTI group was inferior to the other 2 groups at 96 weeks.[24]

Several recent trials were terminated early because of higher virological failure rates of 3-NRTI regimens, including those with tenofovir, abacavir, and lamivudine[36,37] and tenofovir, didanosine, and lamivudine.[38] The mechanisms underlying these failures are unclear, but emergence of the tenofovir-associated K65R mutation was observed in a substantial number of participants. The combination of stavudine, didanosine, and abacavir is also an inferior initial regimen.[39] It should be noted that the virological failure rates in these studies are higher than those seen previously with the combination therapy of zidovudine, lamivudine, and abacavir.[40]

Once Daily Regimens

Many antiretroviral regimens are dosed twice per day, but several drugs are administered once per day. These include efavirenz, tenofovir, didanosine, lamivudine, emtricitabine, stavudine extended release, atazanavir, and the combination of amprenavir and low-dose ritonavir (or the combination of fosamprenavir and low-dose ritonavir in protease inhibitor-naive patients[41]). Abacavir[42] and nevirapine[26] can also be given once daily, but more hepatobiliary toxicity occurred in the 2NN study when nevirapine was taken once daily than when it was taken twice daily.[26] However, few regimens in which all drugs are given simultaneously have been evaluated in randomized studies, and, some once daily drugs cannot be taken simultaneously. In the FTC-301 study,[43] the once daily combination of emtricitabine, didanosine, and efavirenz was superior to the combination of stavudine and didanosine taken twice daily plus efavirenz taken once daily in 571 treatment-naive patients for 24 weeks. In the ZODIAC study,[42] abacavir once daily was not inferior to abacavir twice daily when combined with lamivudine and efavirenz twice daily (plasma HIV RNA <50 copies/mL in 66% and 68%, respectively) in 770 patients at 48 weeks.

Recommendations

A regimen containing an NNRTI is often the regimen of choice for initial antiretroviral treatment when adherence is expected to be good because of convenience, superior virological suppression, lower rates of toxic effects, and fewer interactions between drugs than with boosted protease inhibitor regimens (evidence strength rating, IA; TABLE 4). Of the NNRTIs available, the weight of available data favors efavirenz (evidence strength rating, IA). Nevirapine is a reasonable option (evidence strength rating, IA); potential toxic effects make it less satisfactory in some patients (eg, those coinfected with hepatitis C virus, those with elevated liver enzymes, and women with >250 CD4 cells/μL) (evidence strength rating, IB). Efavirenz is contraindicated in women who are or wish to become pregnant because of the potential teratogenicity (evidence strength rating, IA).[44] Treatment with nevirapine during pregnancy must be monitored carefully for liver enzyme elevations (evidence strength rating, IB). Delavirdine is not generally recommended for initial regimens because of insufficient data.

For initial regimens that include a protease inhibitor, those that are ritonavir boosted are recommended because of the improvement in protease inhibitor pharmacokinetics and potency (evidence strength rating, IA). More data are available for lopinavir/ritonavir (evidence strength rating, IA)[28] than for some other recommended boosted protease inhibitor components (eg, atazanavir and low-dose ritonavir [evidence strength rating, IV], indinavir and low-dose ritonavir, [evidence strength rating, IB], or saquinavir and ritonavir [evidence strength rating, IA]), but it is not clear that lopinavir/ritonavir is the preferred boosted protease inhibitor. Regimens containing lopinavir/ritonavir generally produce durable responses among those who can tolerate ritonavir; virological failure associated with the emergence of resistance is rare. Recommendations concerning the relative merits of lopinavir/ritonavir compared with atazanavir and low dose ritonavir will depend on studies of the durability and potency of regimens containing atazanavir and ritonavir. However, atazanavir is less likely to produce plasma lipid abnormalities. The lower relative potencies of nelfinavir (evidence strength rating, IA), unboosted atazanavir (evidence strength rating, IB), and the combination of fosamprenavir and low-dose ritonavir (evidence strength rating, IB) make these drugs less attractive options for initial regimens. Full-dose ritonavir as the only protease inhibitor component is not generally recommended because of its toxicity profile.

The recommended double NRTI backbones in the initial regimen are zidovudine plus lamivudine or emtricitabine; tenofovir plus lamivudine or emtricitabine; or emtricitabine plus didanosine. Of note, emtricitabine plus didanosine (or alternatively abacavir plus lamivudine) can be used with efavirenz when once daily regimens are necessary. Alternative dual NRTI regimens are listed in Table 3. Combining stavudine and zidovudine is contraindicated; combinations of stavudine and didanosine or combinations with zalcitabine are not recommended because of increased toxic effects (evidence strength rating, IB).

Triple-NRTI regimens are no longer recommended as initial therapy because of insufficient antiretroviral potency compared with a regimen containing efavirenz (evidence strength rating, IA). However, for patients requiring treatment with regimens that

Table 4. Recommended and Alternative Components for Initial Antiretroviral Regimens*

Regimen	Evidence Rating†
Recommended Components	
NNRTI component	
Efavirenz	IA
(Or nevirapine in selected patients)‡	IA
Protease inhibitor component§	
Lopinavir/ritonavir	IA
Atazanavir with low dose ritonavir	IV
Saquinavir with low dose ritonavir	IA
Indinavir with low dose ritonavir	IB
NRTI component‖	
Zidovudine or tenofovir and lamivudine or emtricitabine	
Didanosine and emtricitabine¶	
Alternative Components	
Protease inhibitor component§	
Fosamprenavir with low dose ritonavir	IB
Atazanavir	IB
Nelfinavir	IA
NRTI component	
Abacavir and lamivudine¶	
Didanosine and lamivudine¶	
Didanosine and tenofovir#	
Stavudine and lamivudine¶	
Zidovudine and abacavir	
Special Circumstances Only	
3-NRTI regimen	
Zidovudine, lamivudine, and abacavir**	IA, VII

Abbreviations: NRTI, nucleoside (or nucleotide) reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.
*Generally include a dual NRTI backbone with either an NNRTI or a ritonavir-boosted protease inhibitor. In special circumstances, a triple NRTI regimen (zidovudine, lamivudine and abacavir) may be an alternative regimen.
†See Box for explanation of ratings.
‡See "Recommendations."
§Direct head-to-head comparative studies have not been performed to allow clear determination of the best protease inhibitor.
‖Fewer long-term data are available for tenofovir and emtricitabine.
¶Lamivudine and emtricitabine are considered interchangeable, but confirmatory data are lacking.
#May be associated with more pancreatitis[73] and more CD4 cell count declines.[74] Also see Table 5.
**A triple NRTI initial regimen may be necessary for selected patients.

preclude use of NNRTIs or protease inhibitors, a combination consisting of zidovudine, abacavir, and lamivudine may be considered (evidence strength rating, VII). In these special situations, close HIV RNA level monitoring is mandatory to identify early virological failure. The 3-NRTI regimens that should not be used are: tenofovir, abacavir, and lamivudine (evidence strength rating, IB); tenofovir, didanosine, and lamivudine (evidence strength rating, IB); and stavudine, didanosine, and abacavir (evidence strength rating, IB).

Initial 4-drug regimens (ritonavir at the boosting dose is not considered an additional antiretroviral drug) are not recommended at this time (evidence strength rating, IA). Experimental 2-drug regimens (eg, a boosted protease inhibitor and an NNRTI or a second protease inhibitor) require further study before they can be safely recommended. Monotherapy consisting of a boosted protease inhibitor (eg, lopinavir/ritonavir alone) is not recommended (evidence strength rating, IV). Attention to potential interactions between drugs among all drug components in regimens (first and subsequent ones) is important (TABLE 5), as is caution for the use of combinations that have not been adequately tested in clinical trials or pharmacokinetic evaluations.

WHEN TO CHANGE AND WHAT TO CHANGE TO

Recent Data Addressing These Questions

Changes to the initial antiretroviral regimens are common and most often related to treatment-related toxic effects, intolerance, inconvenience, or failure. Indeed, the median time of an initial regimen is 1.6 years.[16] The recommendations for when to change a regimen and what to change to depend on the reason for changing therapy, whether it is in response to the first treatment or to multiple treatment failure, and the availability of active drugs to construct a potent regimen.

Toxicity, Intolerance, or Inconvenience

Several studies have evaluated switching the protease inhibitor component of a regimen to an NNRTI in patients with plasma HIV RNA levels below detection to reduce metabolic abnormalities and fat maldistribution syndromes.[45] In general, changing therapy is virologically safe in a patient harbor-

Table 5. Interactions Between Antiretroviral Drug Pairs Requiring Dosing Alteration or Avoidance*

Drug 1	Drug 2	Result	Panel Suggestion
Zidovudine	Stavudine	Intracellular antagonism	Do not combine
Stavudine	Didanosine	Toxicity (peripheral neuropathy, lactic acidosis)	Avoid, especially during pregnancy
Lamivudine	Emtricitabine	Similar drugs	Do not combine
Tenofovir	Enteric-coated didanosine	Increased didanosine level[75,76]	Decrease didanosine to 250 mg
Tenofovir	Atazanavir	Increased tenofovir level, decreased atazanavir level	Add ritonavir boosting†
Delavirdine	Amprenavir	Increased amprenavir level[77]	Avoid, or decrease amprenavir dose
Delavirdine	Indinavir	Increased indinavir level[78]	Avoid, or decrease indinavir dose‡
Delavirdine	Saquinavir	Increased saquinavir level	Decrease saquinavir dose
Efavirenz	Indinavir	Decreased indinavir level[79]	Increase indinavir dose‡
Efavirenz	Lopinavir/ritonavir	Decreased lopinavir level[80,81]	Increase lopinavir and ritonavir dose to twice daily
Efavirenz	Nevirapine	Decreased efavirenz level[82]	Not recommended
Efavirenz	Ritonavir	Increased efavirenz and ritonavir levels[83]	Decrease ritonavir dose
Efavirenz	Amprenavir	Decreased amprenavir level[84,85]	Add ritonavir boosting†
Efavirenz	Atazanavir	Decreased atazanavir level	Add ritonavir boosting†
Efavirenz	Saquinavir	Decreased saquinavir level[44]	Add ritonavir boosting†
Nevirapine	Lopinavir/ritonavir	Decreased lopinavir level[86]	Increase lopinavir and ritonavir dose to twice daily
Nevirapine	Indinavir	Decreased indinavir level[87]	Increase indinavir dose‡ or add ritonavir boosting†
Nevirapine	Saquinavir	Decreased saquinavir level	Add ritonavir boosting†
Nelfinavir	Saquinavir	Increased nelfinavir level[88]	Decrease saquinavir dose
Atazanavir	Indinavir	Hyperbilirubinemia	Do not combine
Fosamprenavir or amprenavir	Lopinavir/ritonavir	Decreased amprenavir and lopinavir levels	Avoid unless doses can be adjusted according to plasma concentrations of amprenavir and lopinavir§
Fosamprenavir	Amprenavir	Similar drugs	Do not combine

*Many antiretroviral drugs affect the level of a second agent in the class but not to a degree requiring dose changes or avoidance. There are many important interactions between antiretroviral agents and drugs in other classes, which are not summarized in this table. Certain groups of antiretroviral drugs affect resistance selection resulting in potentially adverse outcomes, but these are not included in this table.
†Dose of ritonavir in boost is not specified.
‡Little or no data exist to define the exact dose adjustment required.
§Data are conflicting. One study suggests no adjustment needed.

ing no archived drug resistance mutations.[46] Hyperlipidemia associated with protease inhibitor use has improved after changing therapy.[45] Switching from a protease inhibitor to nevirapine produced greater declines in cholesterol levels than did changing to efavirenz, and nevirapine was associated with sustained increases in levels of high-density lipoprotein cholesterol. Once a fat maldistribution syndrome has occurred, switching the putatively offending antiretroviral agents may halt further progression of the body shape changes, but usually does not reverse the abnormality or does so slowly.[45,47]

Mitochondrial toxicity is the likely underlying mechanism responsible for the lactic acidosis syndrome associated with NRTIs, with the risk being presumptively related to the differential inhibition of mitochondrial DNA polymerase γ by NRTIs.[48] Stavudine and the combination of stavudine and didanosine appear to pose the greatest risk among NRTIs but lactic acidosis has occurred with zidovudine and other drugs in this class.[48] Few studies have addressed the consequences of switching from a combination of 2 NRTIs and a protease inhibitor or an NNRTI to an NRTI-sparing regimen combining a protease inhibitor and an NNRTI in patients with HIV RNA plasma levels below detection. Preliminary data suggest that switching to a combination of nevirapine, lopinavir/ritonavir[49] or efavirenz, saquinavir and low-dose ritonavir[50] may be virologically safe.

Treatment Failure

Incomplete adherence is the most frequent cause of first virological failure.[1] The benefits of plasma HIV RNA suppression to less than 50 copies/mL on durability of response and prevention of emergence of resistance support using this cutoff as a strict definition of virological failure.[1] However, isolated episodes of intermittent viremia, or blips (transient plasma HIV RNA levels >50 copies/mL), do not predict subsequent virological failure.[51] In patients with more advanced treatment failure and a high level of multidrug resistance in whom a HIV RNA level below 50 copies/mL cannot be achieved, the virological objective of the next regimen shifts to reducing the HIV RNA level by at least 0.5 $\log_{10}$ to 1 $\log_{10}$.[52,53] Maintenance of immunological and clinical integrity then becomes the main objective.

A key to successful management of antiretroviral treatment failure in which drug resistance is suspected or documented is the ability to construct a regimen that contains 3 active drugs; the number of active drugs in a regimen correlates with subsequent virological success.[54] The challenge arises in trying to accomplish this given the increasing recognition of drug class cross-resistance that severely reduces options.

Treatment Interruptions and Intermittent Therapy

Studies are under way to evaluate structured (or supervised) treatment interruptions (STIs), which include intermittent therapy strategies in patients with controlled virus replication while receiving drug therapy. The objective is to determine if several cycles of STIs can reduce the duration of exposure to drug therapy without compromising the CD4 cell count. A potential risk is the emergence of virus resistance to drug therapy.[55]

In patients who had previously received treatment, STI has been proposed to allow "reversion" to wild-type virus. Three randomized trials have shown no benefit to this approach[56-58] and one has reported benefit.[59] Differences in baseline CD4 cell counts, use of multidrug therapy (ie, >6 drugs), and lengths of interruptions may explain these differences.

New Drugs

Since the previous guidelines, 3 new drugs have become available for use in treatment failure.

Enfuvirtide. A subcutaneously administered HIV fusion inhibitor, enfuvirtide was evaluated in 2 large phase 3 trials in patients with advanced HIV disease (median CD4 cell count, 90/μL); in patients with multiple previous and current treatment failures (median, 12 prior antiretroviral drugs); and in patients with a median HIV RNA level of 130 000 copies/mL.[60,61] Patients were randomized to receive an optimized background therapy with or without the addition of enfuvirtide. After 48 weeks, the enfuvirtide group had a significantly greater decrease in HIV RNA level (1.48 $\log_{10}$ reduction) than the optimized background only group (0.63 $\log_{10}$ reduction). With the exception of frequent injection-site reactions, the drug was well tolerated.[60,61] Bacterial pneumonia was more frequent with (6.6%) than without (0.6%) enfuvirtide, and hypersensitivity reactions were rare (<1%). In a secondary analysis of the combined TORO databases, 37.4% in the enfuvirtide group and 16.2% in the optimized background only group had plasma HIV RNA levels below 400 copies/mL at 24 weeks ($P<.001$). Independent of enfuvirtide use, the likelihood of virological response was greater for patients who had a baseline CD4 cell count above 100/μL (odds ratio [OR], 2.4; 95% CI, 1.6-3.5); baseline HIV RNA level below 100 000 copies/mL (OR, 1.8; 95% CI, 1.2-2.6); prior exposure to fewer than 10 antiretroviral drugs (OR, 1.8; 95% CI, 1.2-2.6); and more than 2 additional active antiretroviral drugs in their background regimen (OR, 2.8; 95% CI, 2.0-4.0). Of note, in these analyses, 80% of patients who had all 4 positive prognostic factors had HIV RNA levels below 400 copies/mL at week 24.[54]

Atazanavir. A regimen containing 300 mg/d of atazanavir and 100 mg/d of ritonavir provided viral load reduction at 24 weeks comparable to lopinavir/ritonavir in 1 study,[32] whereas 400 mg/d of atazanavir (unboosted) was inferior to lopinavir/ritonavir.[35] Of note, the combination of atazanavir and low dose ritonavir was associated with less elevation of plasma lipid levels (particularly total cholesterol and triglycerides) than boosted protease inhibitor comparators in treatment-experienced patients.[32] Tenofovir coadministration diminishes the oral bioavailability of atazanavir, and ritonavir

boosting of atazanavir counteracts this negative drug interaction.[62] Thus, when given to treatment-experienced patients or when combined with tenofovir, atazanavir should only be used with ritonavir boosting (evidence strength rating, IB).

Fosamprenavir. A prodrug of amprenavir, fosamprenavir has higher bioavailability and an improved formulation over the parent compound. Fosamprenavir should be administered with low-dose ritonavir (700 mg of fosamprenavir and 100 mg of ritonavir twice daily) (evidence strength rating, IB). In a comparative study, fosamprenavir with low-dose ritonavir taken twice daily had similar activity and tolerability as lopinavir/ritonavir.[63]

Recommendations

Changing Therapy Because of Toxicity, Intolerance, or Inconvenience. Adverse effects of antiretroviral drugs are numerous, ranging from low-grade intolerance to life-threatening reactions. Low-grade and often transient symptoms of high frequency that typically occur early after initiation of therapy (eg, zidovudine-related headache and nausea; efavirenz-related central nervous system adverse effects) can often be mitigated through patient education. When symptoms associated with a particular agent do not resolve, or laboratory toxicity develops (eg, zidovudine-related anemia), single drug substitutions (eg, changing zidovudine to stavudine or changing efavirenz to nevirapine) may be indicated (evidence strength rating, II).

When toxicity cannot be confidently attributed to a single drug and is severe enough to require temporary discontinuation of therapy, all agents in the combination should be stopped (evidence strength rating, VII). If drugs with substantially different half lives are in the regimen (eg, NNRTIs and NRTIs), staggered discontinuation of the drugs should be considered to avert the emergence of drug resistance (evidence strength rating, V). For example, pharmacokinetic data indicate that NNRTIs persist and select for resistance after drug discontinuation.[19,64,65] Stopping nevirapine or efavirenz 5 to 7 days before stopping the NRTI components has been suggested. However, the effectiveness of this approach in averting resistance in the clinical setting needs to be determined.[66] Once the toxicity resolves, a new regimen can often be introduced.[67]

Cycles of STIs in patients with controlled viremia simply to reduce long-term exposure to the drugs are not recommended at this time, nor are intermittent treatment approaches for initial or failing regimens (evidence strength rating, IB).

A difficult toxicity-management question is whether to change therapy in the face of metabolic abnormalities. Hyperlipidemia associated with protease inhibitors sometimes can be managed with diet, exercise, and lipid-lowering agents if the benefit of maintaining the particular protease inhibitor is thought to outweigh the risk of changing therapy.[68] This situation commonly arises in the treatment-experienced patient with a documented drug-resistant virus in whom a protease inhibitor-based regimen has led to successful virological suppression. This contrasts to the clinical circumstance in which a patient with drug-susceptible virus at baseline begins therapy with a protease inhibitor-based regimen and achieves virological suppression, but in whom substantial hyperlipidemia develops. With the latter, switching the protease inhibitor to an NNRTI is often virologically safe and leads to improving the lipid profile.

Fat maldistribution syndromes (including central fat accumulation and peripheral fat wasting) pose particular management challenges because many drugs from different classes are often involved. Given that stopping the responsible drug(s) usually does not reverse the abnormality or does so only slowly,[68] close monitoring for the first signs of body fat changes and early switching, if options exist, is recommended (evidence strength rating, VII).

Symptomatic lactic acidosis is a life-threatening condition for which immediate discontinuation of the antiretroviral regimen is indicated (evidence strength rating, II). Following recovery, the safest course is to introduce an NRTI-sparing regimen, such as a ritonavir-boosted protease inhibitor with an NNRTI. However, lamivudine (and presumably emtricitabine), abacavir, and tenofovir may sometimes be safely reintroduced following full recovery from this syndrome if benefit is thought to outweigh the risk (evidence strength rating, V).[48] Close monitoring is required if this is attempted.

Changing Therapy Because of Treatment Failure. Treatment failure may be defined clinically (HIV-related disease progression), immunologically (declining CD4 cell count), or virologically. Viral rebound should be confirmed to ensure that it is not transient (ie, a blip).

In individuals in whom the first regimen fails and who were infected with drug-susceptible virus, careful attention to adherence is required (evidence strength rating, VII). Supportive questioning about adherence (eg, number of missed doses, reasons for the missed doses, etc) may provide insight into the likely success of the current regimen and create an opportunity for intervention. Assessment of subtle toxic effects ascribed to the drugs is particularly important in ensuring adequate adherence. If attempts at improving adherence fail and plasma HIV RNA levels are confirmed to be higher than 500 copies/mL up to 1000 copies/mL, resistance testing should be obtained (evidence strength rating, II). Full susceptibility to all drugs in the regimen suggests an adherence problem. In this circumstance, the regimen does not need to be changed unless intolerance to or inconvenience of 1 or more components is at the root of the diminished adherence. If drug resistance is detected, altering the regimen is indicated (evidence strength rating, IA). The target for the new therapy is the same as in the treatment-naive patient—to suppress the plasma HIV RNA level below 50 copies/mL (evidence strength rating, VII).

The management challenges increase substantially as subsequent regimen fail-

ures cause further drug resistance and intolerance, and thereby limit the remaining antiretroviral options. If durable undetectable levels of HIV RNA are deemed unachievable, the goal of therapy shifts from preventing resistance (ie, maintaining <50 HIV RNA copies/mL) to maintaining immunological integrity and preventing clinical disease progression. Assuming adherence is optimized and overt clinical disease progression is not present, the following should be evaluated: (1) the antiretroviral drug options that remain based on the results of drug resistance testing and treatment history; (2) the plasma HIV RNA level; and (3) the CD4 cell count. If a new regimen that contains at least 2 or 3 active drugs can be constructed, strong consideration should be given to a change so that further drug resistance compromising entire drug classes does not evolve (evidence strength rating, IA). If, however, such a regimen cannot be constructed, changing therapy can be deferred, unless the imminent risk of an opportunistic disease is deemed high.

When resistance to and toxicity of NRTIs or NNRTIs limits the availability of nonprotease inhibitor drugs, use of a double-boosted protease inhibitor (2 active protease inhibitors and low-dose ritonavir) has been proposed for study. Despite the frequent use in clinical practice, the paucity of data for most multiprotease inhibitor combinations in terms of pharmacokinetic interactions, tolerance, or long-term adverse effects warrants extreme caution. For example, coadministration of lopinavir/ritonavir with fosamprenavir causes lowered concentrations of both lopinavir and fosamprenavir. This also illustrates the importance of having sufficient pharmacokinetic data to support dosing in clinical practice and a possible role for therapeutic drug level monitoring in patient management. There are, however, insufficient data other than from pilot testing to recommend therapeutic drug monitoring at this time.

A special area for consideration of regimen change is in the type of discordant response in which the HIV RNA level is below the limit of detection but the CD4 cell count response is blunted. Current medications should be reviewed for potential hematologic toxicity that also may be responsible for the blunted CD4 cell response. Changing or intensifying the regimen has not been shown to have an effect on the CD4 cell count response. The use of interleukin 2 in this setting remains a research question only. The role of STIs for managing multiple failure requires more study, and they are not recommended at this time.

Role of New Drugs in Treatment-Experienced Patients. The optimal time to use enfuvirtide in treatment-experienced patients involves considering its inconvenience, which is generally acceptable in patients with a limited number of alternative options, and its high cost. Enfuvirtide is best considered at the time of the second, third, or fourth failure, depending on the number of active drugs that remain as options (evidence strength rating, IA). The cost and need for subcutaneous administration often contribute to delayed use of this drug to a point when outcome may be compromised by the inability to combine it with other active drugs. If enfuvirtide is to be used, incremental, functional monotherapy should be avoided whenever possible (evidence strength rating, IB). Among patients who have achieved an undetectable plasma HIV RNA level, there is no evidence that enfuvirtide can be discontinued without resulting in a viral rebound.

Available data suggest that atazanavir should be boosted with ritonavir when used in treatment-experienced patients (evidence strength rating, IV). The role of atazanavir in multiple treatment failure is unknown. Similarly, fosamprenavir should be boosted and given twice daily, especially in the setting of multidrug-resistant virus. The use of either drug in this setting should be guided by resistance testing results (evidence strength rating, IA).

Management of antiretroviral treatment failure and multidrug resistance may also involve the use of investigational drugs through clinical trials. Physicians specializing in the treatment of HIV should remain cognizant of drugs in development that may become available. These drugs may provide additional options for constructing effective regimens and may influence the timing of a change in therapy.

Monitoring Antiretroviral Therapy. Clinical, CD4 cell count, and plasma HIV RNA level monitoring remain tools in assessing the need for and the response to therapy and recommendations have not changed.[1] Maximal adherence to the chosen regimen is crucial to the success of antiretroviral therapy and attention to adherence is required.[1] Routine drug resistance testing should be used in treatment-naive and treatment-experienced persons as recommended.[69] Viral replicative capacity, which can be impaired by drug resistance mutations, may in some patients result in prolonged elevations of CD4 cell counts in the setting of apparent virological failure. Although commercially available, it is not yet known if replicative capacity adds substantial information to routine clinical and laboratory monitoring. Therapeutic drug monitoring is performed frequently in certain countries, but its role in clinical practice remains controversial. Experimental monitoring for toxicity predilection, such as human leukocyte antigen typing for abacavir hypersensitivity risk[70] or mitochondrial DNA quantitation for NRTI risks, requires further validation.

CONCLUSIONS

Antiretroviral therapy remains a rapidly evolving and challenging area of HIV medicine. The field will continue to evolve with additional insights into pathogenesis and new drug development. With respect to the latter, new agents in existing drug classes (eg, D-D4FC, SPD-754, TMC-125, tipranavir, TMC-114) and in new drug classes (eg, CCR5 inhibitors, integrase inhibitors, maturation inhibitors) that have reached the clinical testing phase provide hope that new options will be available over the next few years.

Clinicians and patients are confronted with the contrast of the increasingly complex individualization of treatment in the developed world and the massive antiretroviral implementation programs that are planned or ongoing in the developing world. The principles of pathogenesis and treatment learned in both settings can ultimately contribute to improved care for all.

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Dr Katzenstein holds a US patent for polymerase chain reaction assays monitoring antiviral therapy and making therapeutic decisions in the treatment of AIDS. Dr Montaner holds 2 US patents, one regarding use of nevirapine and another regarding pharmacological applications of mitochondrial DNA assays. Dr Montaner has 2 patent applications that are pending, one regarding pharmacological applications of mitochondrial DNA assays and another regarding sepsis.

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