Antiretroviral Treatment for Adult HIV Infection in 2002

Updated Recommendations of the International AIDS Society-USA Panel

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Objective New information warrants updated recommendations for the 4 central issues in antiretroviral therapy: when to start, what drugs to start with, when to change, and what to change to. These updated recommendations are intended to guide practicing physicians actively involved in human immunodeficiency virus (HIV)– and acquired immunodeficiency syndrome (AIDS)–related care.

Participants In 1995, physicians with specific expertise in HIV-related basic science and clinical research, antiretroviral therapy, and HIV patient care were invited by the International AIDS Society-USA to serve on a volunteer panel. In 1999, others were invited to broaden international representation. The 17-member panel met regularly in closed meetings between its last report in 2000 and April 2002 to review current data. The effort was sponsored and funded by the International AIDS Society-USA, a not-for-profit physician education organization.

Evidence and Consensus Process The full panel was convened in late 2000 and assigned 7 section committees. A section writer and 3 to 5 section committee members (each panel member served on numerous sections) identified relevant evidence and prepared draft recommendations. Basic science, clinical research, and epidemiologic data from the published literature and abstracts from recent (within 2 years) scientific conferences were considered by strength of evidence. Extrapolations from basic science data and expert opinion of the panel members were included as evidence. Draft sections were combined and circulated to the entire panel and discussed in a series of full-panel conference calls until consensus was reached. Final recommendations represent full consensus agreement of the panel.

Conclusions Because of increased awareness of the activity and toxicity of current drugs, the threshold for initiation of therapy has shifted to a later time in the course of HIV disease. However, the optimal time to initiate therapy remains imprecisely defined. Availability of new drugs has broadened options for therapy initiation and management of treatment failure, which remains a difficult challenge.

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PROGRESS IN ANTIRETROVIRAL therapy has resulted in achievements as well as new challenges.[1] The partial restoration of CD4 and CD8 T cell number and function during suppression of human immunodeficiency virus 1 (HIV-1) replication with potent antiretroviral therapy has resulted in dramatic reductions in morbidity, mortality, and health care utilization.[2-4] However, the toxicity of many current regimens, suboptimal activity and tolerability, and the emergence of drug resistance all point to the need for treatment strategies to

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address these challenges. These strategies include both new antiviral drugs and approaches to enhance host cellular immune control of HIV replication. This evolution in the field prompts the need for a reevaluation of current treatment guidelines, particularly regarding when to initiate therapy. The changing threshold for initiating therapy that has been emerging[1,5] is the result of recognition of limitations of currently available agents and is not necessarily a reflection of a major change in our understanding of disease pathogenesis, nor an indication that more aggressive treatment approaches should not be pursued. This is a constantly evolving field and HIV/AIDS (acquired immunodeficiency syndrome) practitioners will need to keep pace with current knowledge.

METHODS

The International AIDS Society-USA volunteer antiretroviral panel was convened in 1995 to develop treatment recommendations. The panel's goal was to develop current recommendations for use of antiretroviral therapy in the developed world. The panel included physicians with expertise in HIV-associated basic science, clinical research, and patient care. It was expanded in 1999 to broaden its international representation.

The full panel convened in late 2000 to review new data affecting its previous recommendations[1] and assign committees for 7 sections: rationale, when to initiate therapy, initial regimens, treatment interruptions, monitoring therapy, changing therapy, and adjuvant therapy. A section writer and 3 to 5 section contributors were appointed (each panel member served on numerous sections) for each section. Each section committee met to identify relevant data and prepare draft recommendations for the sections, which were reviewed and discussed by the full panel. Data from the published literature and abstracts from recent scientific conferences were considered. Evidence strengths were considered according to parameters such as type of study (eg, randomized prospective trial, cohort data, case reports), number of subjects, duration of follow-up, and publication source. For example, published prospective studies with more than 20 patients and more than 48 weeks of follow-up were given high priority. Evidence from abstracts from scientific meetings that had not been published within 2 years of presentation were generally excluded. Extrapolations from basic science data and expert opinion of panel members were included as evidence. Draft sections with supporting data and preliminary recommendations were combined and circulated to the entire panel and discussed in a series of full-panel conference calls. The panel chair and vice-chair obtained group consensus on recommendations and they or section writers revised the report as necessary after each panel meeting or conference call. Recommendations herein are made by full-panel consensus agreement.

WHEN TO INITIATE ANTIRETROVIRAL THERAPY

Rationale for Treatment in Established HIV Infection

Highly active antiretroviral therapy (HAART) is usually effective in rapidly reducing plasma HIV RNA levels (ie, viral load) in antiretroviral-naive patients, accompanied by a gradual increase in CD4 cell counts, sometimes to normal levels.[6] The number of memory CD4 cells increases early after effective treatment, as a result of redistribution from lymphoid tissues to the circulation.[7] Naive CD4 cells, which are essential for responses to new antigenic challenges, are restored gradually with ongoing effective suppression of viral replication.[8] For many antiretroviral-naive patients, CD4 cell counts increase to levels at which the patients are no longer generally susceptible to serious opportunistic infections.[3] Because currently available antiretroviral regimens will not eradicate HIV,[9,10] the goal of therapy is to durably inhibit viral replication so that the patient can attain and maintain an effective immune response to most potential microbial pathogens.[11]

Considerations in Initiating Therapy in Asymptomatic Infection

Recent cohort data have provided support for the CD4 cell count being the major determinant of initiating therapy.[12,13] These studies have shown an increased mortality when antiretroviral therapy is initiated in patients with CD4 cell counts below 200/μL compared with initiation at higher levels. It is clear, therefore, that antiretroviral therapy should not be delayed until the patient is at high risk for serious opportunistic diseases (ie, at a CD4 cell count ≤200/μL).[12-15]

The CD4 cell level above 200/μL at which to initiate therapy remains unclear. Some serious illnesses, especially active tuberculosis and bacteremic pneumonia, may occur when the CD4 cell count is above 200/μL.[16-20] In addition, the immune reconstitution syndrome and its associated morbidity may be observed in some patients starting antiretroviral therapy at low CD4 cell counts.[21] Furthermore, some laboratory markers show lower rates of favorable responses when antiretroviral therapy is delayed until the 200 cells/μL threshold is reached. These include less rapid increase in CD4 cell count and potentially decreased ability to reduce viral load to below the limit of detection.[12,15,22-25] Finally, the genetic complexity of HIV in persons increases with time, and this may facilitate escape from host immune defenses.[26] These considerations support use of a CD4 cell count threshold higher than 200/μL. However, there are no definitive data with clinical end points that define at which level above 200 CD4 cells/μL antiretroviral therapy is best started. The available data from cohort studies, with one exception,[27] have not been able to define a CD4 stratum above 200 cells/μL at which patients benefit from initiation of therapy.[12,13] Inherent biases that occur with cohort studies, which are observational and not randomized, and relatively limited follow-up in the studies

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

Disease Type	Recommendation
Symptomatic HIV disease	Treatment recommended
Asymptomatic HIV disease, ≤200 CD4 cells/μL	Treatment recommended
Asymptomatic HIV disease, >200 CD4 cells/μL	Treatment decision should be individualized; recommendations are based on: CD4 cell count and rate of decline† HIV RNA level in the plasma‡ Patient interest in and potential to adhere to therapy Individual risks of toxicity and drug-drug pharmacokinetic interaction

*HIV indicates human immunodeficiency virus.
†Some clinicians and guidelines use a CD4 count threshold of 350 cells/μL to initiate therapy;[5] a high rate of CD4 cell count decline is >100 cells/μL per annum.[30]
‡A high HIV RNA level is above 50 000-100 000 copies/mL.[31]The frequency of CD4 cell measurements before therapy is initiated may be guided by the plasma HIV RNA level.

reported to date (2 to 3 years), mean that conclusions from the analyses must be interpreted with caution. However, these are the best data available, there is general consistency across most studies, and it is questionable whether a randomized trial to study the issue of when to start therapy will ever be feasible.

In persons with CD4 cell counts above 350/μL, risk of 3-year clinical progression is low[28] and additional concerns about impact of antiretroviral regimens on quality of life, risk of serious adverse drug effects, and limitations on future treatment options generally outweigh the benefits of durable viral suppression. However, it should be noted that roughly a third or more of persons have no treatment-limiting adverse effects for at least 3 years after initiation of treatment, leaving an option to physicians and patients to initiate therapy at higher CD4 cell counts.[29] For persons who have already initiated therapy at higher CD4 cell count thresholds (eg, 400, 450, or 500 cells/μL) and have had durable HIV RNA suppression and no adverse effects over periods of months to years, it is not clear whether it is safe to discontinue therapy. Physicians and patients must thoroughly weigh risks and benefits of starting antiretroviral therapy for CD4 cell counts in the 200/μL to 350/μL range and above, and make individualized informed decisions (TABLE 1).[5,30,31] The strength of the recommendation should depend on the immunologic status, as well as the patient's understanding of and commitment to an often complex regimen.

Although available data supporting the use of a specific viral load threshold as an independent indicator for initiating therapy are scarce,[31] patients with CD4 cell counts at any level who have a viral load above 50 000 to 100 000 copies/mL[31] should be closely monitored, because the CD4 cell count decreases more rapidly in untreated persons with higher viral loads.[28,31] Initiation of therapy may be considered in individuals with a viral load above 50 000 to 100 000 copies/mL,[31] or a rapidly declining CD4 cell count even if it is above 350/μL. Some observational studies indicate that viral load early in the course of HIV disease is lower in women than in men, but there are no documented sex differences in the relation of CD4 cell count to risk of opportunistic infections.[32,33] Thus, treatment recommendations are the same for women as for men.

Therapy continues to be recommended in all patients with symptomatic established HIV infection. Immediate treatment, but not prophylaxis, of a serious opportunistic infection in patients with advanced HIV disease may take precedence over starting antiretroviral therapy. If potential for adverse drug-drug interactions exists (eg, protease inhibitors [PIs] and rifampin in treatment of *Mycobacterium tuberculosis* infection), it is wise to choose drugs with minimal or no interactions, or to delay antiretroviral treatment for a few weeks, until drugs causing the interactions can be discontinued. Clinicians should be aware of risk of immune reconstitution illness associated with initial increase in CD4 cell counts in patients starting antiretroviral therapy when there is a confirmed or suspected opportunistic infection.[21]

ESTABLISHED INFECTION: INITIAL THERAPY

Choice of Initial Therapy

No drug combination can be defined as the optimal initial regimen in all patients. Therapy should thus be individualized using a number of criteria, including efficacy and durability of antiretroviral activity, tolerability and adverse effects (TABLE 2),[34-84] convenience of the regimen, drug-drug interactions, and potential salvageability of initial regimen.

The differences in "clinical activity" that are observed in clinical trials between regimens that contain 2 nucleoside reverse transcriptase inhibitors (NRTIs) with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a single (or boosted) PI are often too small to differentiate relative efficacy. The durability of the first regimen is primarily related to issues of adherence, tolerability, and convenience, and baseline virological or immunologic status. Drugs with long half-lives and those for which regular timing of food or hydration is less crucial are likely to have an advantage. Daily adverse effects, even if minor, may reduce adherence. Finally, concerns for long-term toxic effects may be an important cause of patient reluctance to take certain medications. Regimens that involve drugs taken twice a day are likely to be associated with better adherence than those involving drugs taken 3 or more times a day.[85] Once-daily regimens may further facilitate adherence and permit directly observed therapy in individual circumstances.

Many patients will ultimately experience at least one treatment failure. Because the initial regimen affects choices available for subsequent regimens, consideration should be given to such issues as overlapping toxicities (eg, with

Table 2. Monitoring and Management of Selected Toxic Effects and Adverse Complications of Antiretroviral Therapy*

Toxicity/Definition	Etiology/Drug Association	Clinical/Laboratory Signs and Symptoms	Screening/Monitoring	Management	Comments
Lactic acidemia: asymptomatic (>10 mmol/L) and symptomatic (5-10 mmol/L)[34,35]	Caused by NRTI-induced mitochondrial dysfunction?[36] Associated with all NRTIs[37-40]; stronger association with stavudine suggested but not yet confirmed.[41] Associated with stavudine/didanosine combination in pregnant women.[42,43]	Clinical: nausea and/or vomiting, fatigue, abdominal pain, weight loss, dyspnea, with/without signs of liver failure[37,39-41] Laboratory: increased serum lactate, decreased serum bicarbonate, increased anion gap, with/without modest increased LFT results[41]	Routine lactate monitoring not recommended. Lactate levels are unreliable unless drawn according to established guidelines. Increased values should be repeated for confirmation.	Lactate >5 mmol/L with symptoms, or lactate >10 mmol/L: discontinue all ART immediately Asymptomatic, lactate >5 mmol/L without symptoms (confirmed by repeat testing): consider ART discontinuation Asymptomatic, lactate 2-5 mmol/L: monitor	Potentially fatal; early clinical suspicion is vital. Safety of NRTI reintroduction after resolution is not known. Mild asymptomatic lactic acidemia (confirmed by repeat testing) may have a positive predictive value for the development of lactic acidosis.[44]
Lipid Abnormalities Triglyceride level increases LDL level increases	Association with all PIs; may be strongest with ritonavir[45-52] Association with NNRTIs unclear and contradictory[53]		Assess fasting LDL, HDL, total cholesterol, and triglyceride levels at baseline, 3-6 months after ART is started or changed, and annually thereafter. If pharmacological intervention is started, monitor every 3-6 months.	Follow guidelines using Framingham risks[54-56] with attention to potential drug-drug interaction,[57-59] if pharmacological intervention is considered.	Very high triglyceride levels may be associated with pancreatitis risk.[60] Switching PI component to nevirapine or abacavir is possible, although supporting data are not conclusive.[53]
Glucose intolerance, insulin resistance, type 2 diabetes	Suggested associations with PIs; also with PI-sparing regimens[61-63]		Fasting glucose levels recommended prior to ART initiation, and every 3 to 6 months after institution of a PI. Routine oral glucose tolerance testing not recommended.	Emphasize diet, exercise, and weight loss. Pharmacological interventions (oral hypoglycemic agents, insulin-sensitizing agents, insulin) should follow guidelines per non–HIV-infected populations. Attention to potential drug-drug interactions is warranted if pharmacological intervention is considered.	
Body fat composition abnormalities	Initially described in association with PIs; noted in non-PI regimens.[45,64,65]		No clear recommendations for screening/monitoring can be made: CT or MRI scans, DXA, and ultrasound are research tools only. Anthropometric measurements lack standardization and reproducibility. BIA is not useful. However, serial waist/hip (or waist alone) and breast measurement in women may be helpful documentation.	No established treatment.	Lack of syndrome definition and standardized measurement methodology makes prevalence estimates difficult.
Hepatitis/hepatotoxicity	Associated to some degree with all ART. Coinfection with hepatitis B or C virus may increase risk.[66] Severe or fatal hepatotoxicity reported with nevirapine,[67] and in 3 pregnant women on didanosine/stavudine.[68]		For patients taking nevirapine, monitor LFT results at baseline, prior to dose increase, and 2 weeks after dose increase. Aggressively monitor LFT results and electrolytes in pregnant women taking didanosine/stavudine.[69]		Didanosine/stavudine should be avoided or used cautiously in pregnant women.

(continued)

PIs in the case of lipid abnormalities or with some NRTIs in the case of neuropathy) and intraclass cross-resistance (see "First or Second Failure" section). There are currently no data on preferred sequencing of NRTIs. Stavudine and didanosine in combination should be avoided or used with caution in pregnant women because of increased risks of lactic acidosis.[86]

There are generally 3 types of initial combination regimens that should be considered: (1) a PI (with or without low-dose ritonavir) with 2 NRTIs; (2) an NNRTI with 2 NRTIs; or (3) 3 NRTIs. Other regimen combinations include a PI (with or without low-dose ritonavir) with an NNRTI plus 1 or 2 NRTIs, which should be reserved for special circumstances; and a PI (with low-dose ritonavir) with an NNRTI (see below).

Protease Inhibitor–Based Regimens. Data from randomized controlled trials with clinical outcomes attest to the effectiveness of PIs in combination with NRTIs.[87] However, some regimens containing single PIs are often difficult to adhere to because of 3-times-a-day regimens or food con-

Table 2. Monitoring and Management of Selected Toxic Effects and Adverse Complications of Antiretroviral Therapy* (cont)

Toxicity/Definition	Etiology/Drug Association	Clinical/Laboratory Signs and Symptoms	Screening/Monitoring	Management	Comments
Bone demineralization and avascular necrosis	Definitive association with HIV itself, ART, and PIs unclear.[70-76] Duration of ART use and history of steroid use are risk factors.[77]		Bone density assessments not recommended except for patients already at risk for osteoporosis or osteopenia. Patients with symptoms of avascular necrosis should have CT scan performed.	Treatment for osteopenia should be in accordance with extent of bone loss. Interventions should be similar to those in non–HIV-infected populations.	
Drug hypersensitivity	Associated with all NNRTIs,[78-80] amprenavir,[81,82] and abacavir.[83,84]	NNRTIs: serious rashes (including Stevens Johnson reaction) have occurred.[78-80] Abacavir: serious/fatal hypersensitivity reaction occurs with or without rash plus constellation of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhea, abdominal pain, pharyngitis, cough, and dyspnea.[83,84]	Patients should be informed of the possibility of a hypersensitivity reaction.	Mild to moderate: generally managed with antihistamines. Severe: stop administration of drug	Challenges after suspicion of drug hypersensitivity reaction not recommended, particularly with abacavir.

*NRTI indicates nucleoside reverse transcriptase inhibitor; LFT, liver function test; ART, antiretroviral therapy; LDL, low-density lipoprotein cholesterol; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; HDL, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; CT, computed tomography; MRI, magnetic resonance imaging; DXA, dual-energy x-ray absorptiometry; and BIA, bioelectrical impedance analysis.

straints (eg, indinavir), or large pill burdens (eg, nelfinavir and amprenavir). Nelfinavir can be taken twice a day, but it is absorbed best when administered with a fatty meal.[88]

Data on benefits of PIs, in combination with low-dose ritonavir to provide a pharmacokinetic boosting effect, are appearing in studies in treatment-naive patients.[89] Low-dose ritonavir can pharmacologically enhance (or boost) saquinavir, indinavir, amprenavir, or lopinavir (the latter available only in a coformulated capsule).[90] Ritonavir inhibits enzymes of the cytochrome P450 system; it may act early on absorption and first-pass metabolism, increasing peak plasma concentrations with a coadministered PI (eg, with indinavir or amprenavir); or it may inhibit subsequent metabolism and extend the half-life of the second PI with an increase in trough level of drug (eg, with lopinavir or saquinavir). Such considerations may be important for drugs for which toxicity is related to peak concentrations and risks of virological failure to low trough levels. Advantages of such regimens include once- or twice-daily dosing and minimization of specific food requirements. Nelfinavir is not sufficiently enhanced by low-dose ritonavir to justify this combination.[91]

There are no comparative studies to determine which boosted PI regimen has the highest level of activity. Also, optimal dose of the PI or ritonavir in such a combination is often not well defined. Higher doses of ritonavir (eg, >100 mg twice a day) in the combination may result in a higher incidence of gastrointestinal adverse effects and lipid abnormalities.[92] Little is known about optimal alternative regimens when initial boosted PIs fail.

Specific Ritonavir-Enhanced Protease Inhibitor–Containing Regimens. Lopinavir/ritonavir is an important new addition to the list of approved agents. In one study (48-week analysis), lopinavir/ritonavir plus 2 NRTIs were superior to nelfinavir plus 2 NRTIs in reducing viral load to below 50 copies/mL.[93] Grade 3 or 4 elevations in triglyceride levels are significantly more common with lopinavir/ritonavir than with nelfinavir, and high frequencies of grades 3 and 4 cholesterol and triglyceride abnormalities (up to 30%) have been seen when lopinavir/ritonavir is combined with NRTIs and NNRTIs in salvage regimens.[94] There have been few virological failures of lopinavir/ritonavir-containing regimens in studies of treatment-naive patients. Thus, there are few data on the patterns of resistance associated with this drug when used in an initial regimen or to guide recommendations on the preferred alternative regimens after lopinavir/ritonavir has failed. Early failures are associated predominantly with the lamivudine-associated M184V mutation when this agent is part of a lopinavir/ritonavir–containing regimen,[95] an observation similar to what has been reported with indinavir and amprenavir.[96-98]

Indinavir/ritonavir (800 mg/100 mg, respectively, twice a day) may be widely used, but it is unclear whether this is the optimal dose combination, or if, for example, 800 mg/200 mg or 400 mg/400 mg is preferable. Incidence of renal adverse effects including stones, flank pain, and hematuria was higher (up to 20% at 24 weeks) in patients who had been treated previously with indinavir 800 mg 3 times a day and were then switched to indinavir/ritonavir.[99]

Saquinavir 800 or 1000 mg plus ritonavir 100 mg twice a day may be often used because of the adverse effects that are associated with a higher dose of ritonavir (200 mg twice a day), but there is little published comparative experience with this regimen. The pill burden is high if the soft gel saquinavir formulation is used. Ritonavir/saquinavir 400 mg/400 mg, twice a day, has also

been used[100]; in this regimen, ritonavir provides antiretroviral activity as well as pharmacoenhancement. Whether this increases the likelihood of reducing viral loads to below the limit of detection remains unclear. The 24-week, intent-to-treat analysis of a once-daily regimen containing saquinavir (1600 mg, soft gel formulation) plus ritonavir (100 mg) showed that it was virologically inferior to an efavirenz-containing regimen, but the saquinavir/ritonavir group had a higher rate of gastrointestinal adverse effects.[101]

Combining amprenavir with ritonavir increases trough levels of amprenavir[102] and reduces amprenavir pill burden from 16 to 8 pills a day. Given the tolerance profile and high pill burden of amprenavir, and effectiveness of amprenavir-containing combinations after prior PI regimens have failed, use of this combination may be preferred in the treatment-experienced setting.

Nonnucleoside Reverse Transcriptase Inhibitor–Based Regimens. A triple-drug regimen that includes an NNRTI and 2 NRTIs is one of the preferred combinations for initial therapy of established infection, given the effectiveness and the PI-sparing aspect. Three NNRTIs are currently approved in the United States: nevirapine, delavirdine, and efavirenz. No major trials have yet directly compared these drugs. Delavirdine is less often used because of its high pill burden and 3-times-a-day dosing, but it is the only currently available NNRTI that inhibits cytochrome P450, allowing a reduction in the dose of associated PIs.[103,104]

Nevirapine has been studied in the ATLANTIC trial, which compared an NNRTI-based regimen with a PI-based regimen and a triple NRTI-based regimen.[105] Although not powered to provide definitive conclusions, the results suggested that activity of nevirapine in a multidrug regimen was similar to that of indinavir. Comparability in viral suppression at 36 weeks between nevirapine-containing and nelfinavir-containing regimens (each with 2 NRTIs) has been reported.[106] Nevirapine has been associated with severe rashes more often than has efavirenz.[107,108] Use of corticosteroids has not had a beneficial effect.[109] Hepatotoxicity, including elevation of transaminases, jaundice, and rare cases of severe clinical hepatitis, occurs with nevirapine more often than with efavirenz.[107,108] Recently, nevirapine has been shown to be associated with favorable changes in lipid profiles, which include decreases in cholesterol and triglyceride levels and increases in HDL levels in patients who discontinued PIs.[110]

In an open-label study, zidovudine/lamivudine/efavirenz produced a marker response equivalent or superior to that seen with a similar NRTI backbone given with indinavir for up to 96 weeks of follow-up.[111] Efavirenz is commonly prescribed because of its once-daily dosing and safety profile.[108] Because of teratogenicity in animals,[108] efavirenz should be avoided in women who are (or intend to become) pregnant. Hyperexcitability, vivid dreams, nightmares, and hallucinations are associated with efavirenz.[108] Mood disturbances and personality changes may be persistent in some patients.[108]

Triple-NRTI Regimens. Triple-NRTI regimens have become a viable alternative as initial therapy. The largest body of evidence at present is for regimens that contain abacavir. An abacavir/zidovudine/lamivudine combination produced a decrease in viral load (to <400 copies/mL) at 48 weeks equivalent to that produced by zidovudine/lamivudine/indinavir in a placebo-controlled trial.[112,113] However, more complete viral suppression (assessed with an assay with a limit of detection of 50 copies/mL) was less likely with the 3-NRTI regimen in those patients with a pretreatment viral load above 100 000 copies/mL.[112,113] Thus, these regimens are not routinely recommended as initial treatment for patients with high viral loads (eg, >100 000 copies/mL) or with low CD4 cell counts until more data are available. The twice-daily regimen, low pill burden, few daily toxic effects, and lack of undesirable pharmacokinetic interactions are potential advantages of zidovudine/lamivudine/abacavir regimens. Availability of these 3 drugs in a fixed-dose combination is also likely to facilitate adherence. Severe hypersensitivity reactions to abacavir occur in about 3% of patients,[114,115] and is an important consideration.

A virus mutation at codon 184 substantially reduces sensitivity to lamivudine and somewhat (2- to 4-fold) to abacavir. This mutation is often detected during virological failure with abacavir-containing regimens.[116,117] In most such patients,[117] viral mutations associated with resistance to zidovudine are not detected, and in theory other NRTIs would be effective in subsequent regimens. However, continuing treatment with this 3-drug combination, despite the presence of detectable HIV, may be accompanied by development of other NRTI-associated mutations.

Protease Inhibitor/NNRTI–Based Regimens, With or Without NRTI. The combination of a PI with an NNRTI and an NRTI (ie, drugs from all 3 classes), is not routinely recommended because the risks of multiclass drug resistance (thus limiting future treatment options) and toxicity may be high. However, in the setting of a patient with advanced disease and a high near-term mortality risk who has an opportunistic infection for which no effective therapy exists (eg, cryptosporidiosis), a 3-class regimen may be considered to assure a high degree of activity and to try to achieve rapid immunologic restoration. Simplification of such a regimen can be considered subsequently. The second setting in which to consider a 3-class regimen is when the patient is infected with a drug-resistant strain whose in vitro resistance testing profile suggests that such a regimen may be effective.

Protease inhibitor (enhanced with low-dose ritonavir) and NNRTI regimens without an NRTI component may be of interest for certain settings; however, insufficient data exist on when to recommend such NRTI-sparing regimens as initial therapy.

TREATMENT INTERRUPTIONS

Structured, supervised, or strategic treatment interruptions (STIs) have been considered in very different situations: following early therapy of acute HIV syndrome,[118] following suppressive antiretroviral therapy of established infection,[119-121] and for facilitating salvage after therapy has failed.[122] The rationales for interruption of therapy in these 3 settings are different, and the subject has been extensively reviewed elsewhere.[123,124] Given the paucity of available controlled studies and the potential risks, STIs cannot be recommended for current clinical practice, and should preferably be attempted in the context of cohort studies or clinical trials.

MONITORING ANTIRETROVIRAL THERAPY

Adherence: Assessment and Reinforcement

Incomplete adherence to one or more prescribed medications is a key cause of virological failure of antiretroviral regimens.[125] A recent study found a doubling of the viral load for every 10% decrement from complete adherence.[126] In another study, the viral load response was greater in inmates in a prison where treatment was directly observed than in patients treated with comparable regimens in an outpatient research clinic (85%-100% vs 50%-80%).[127,128] Factors that limit full adherence are complex and incompletely defined but may include high pill number and large pill size, medication schedule and dietary restrictions, toxic adverse effects, and ineffective education and support of patients regarding adherence. Progress in developing new drug formulations (eg, didanosine without the buffer) and fixed-dose combinations (eg, lamivudine/zidovudine/abacavir, lamivudine/zidovudine, and lopinavir/ritonavir) that can simplify regimens is encouraging.

Ways of improving adherence are being investigated.[129] Most remain largely empiric and not evidence-based.[129] Effective communication between patient and provider is essential both before and after treatment has begun. Some health care centers may use nonphysicians (pharmacists, nurses, peer educators, and others) to effectively assess and support adherence, but the physician should also be actively involved. Once treatment has begun, weekly contact may be appropriate until the patient has established a consistent daily routine of medication use and has passed the time that any short-term adverse effects would be expected. Reinforcing the need for adherence at every health care provider contact is important.

CD4 Cell Counts and Viral Load

In the asymptomatic individual, antiretroviral activity is evaluated by assessing changes in CD4 cell count and viral load. A decrease in viral load (indicating a reduction in virus replication) and increase in CD4 cell count (indicating an improvement in immune competence) in response to antiretroviral drugs are both associated with clinical efficacy.[130-132]

The CD4 cell count typically increases by more than 50 cells/μL at 4 to 8 weeks after antiretroviral therapy has been started or changed, followed by an additional increase of 50 to 100 cells/μL per year thereafter.[133,134] Once CD4 cell counts exceed 200/μL for 3 to 6 months, there are reduced risks of many opportunistic infections and prophylaxis against certain pathogens can often be stopped.[17]

Current HIV RNA tests have reliable detection limits of about 50 copies/mL, and quantification using commercial tests is reliable at 200 copies/mL.[5] With repeated measurements, differences of 0.2 to 0.3 $\log_{10}$ (30% to 50%) are considered significant evidence of a change in viral load.[135] Virologically effective therapy generally reduces viral load by more than 90% (ie, a 1-$\log_{10}$, or 10-fold, reduction) within 8 weeks of treatment.[136,137] Failure to attain a 90% reduction by 4 weeks of therapy suggests poor adherence, viral resistance, or inadequate drug exposure.

On initiation of therapy, sequential measurements of CD4 cell count and viral load at 4, 8 to 12, and 16 to 24 weeks have been used to assess the early response to antiretroviral therapy.[138-140] A continued decline in viral load at each measurement, together with an increase in CD4 cell count, indicates a drug combination is appropriately active in vivo, and indirectly indicates patient adherence and baseline viral susceptibility. In some instances CD4 cell counts might not increase, or may decrease, with successful suppression of viral replication (HIV RNA, <50 copies/mL).[141] Reasons for this phenomenon are not well understood. Drug-related toxic effects and ongoing opportunistic disease should be investigated. Although no specific intervention has been studied well enough to be recommended at this time, it is important to monitor viral load and CD4 cell counts more frequently in patients with such discordant responses.

Once virological suppression has been achieved (2 sequential measurements below the limit of detection of the most sensitive assay available), viral load and CD4 cell numbers are usually monitored every 8 to 12 weeks.[142] More frequent monitoring may be appropriate in case of intercurrent illness, change in antiretroviral therapy, introduction of a new treatment that could interfere pharmacologically with antiretroviral drugs, or if adherence to therapy becomes questionable. Frequent monitoring may show, even in patients with drug-sensitive virus who report optimal adherence, occasional small increases in detectable plasma virus (blips) in the range of 50 to 400 copies/mL. There is no evidence to date that such isolated blips are predictive of subsequent overt treatment failure.[143]

Drug Resistance Testing

Guidelines for use of drug resistance testing in clinical practice have been published.[144-146] Randomized, prospective trials have demonstrated variable results with respect to short-term virological benefit of genotype or phenotype testing.[147-153] Results of studies showing no difference between study groups may have been affected by the interpretation of the resistance information, par-

ticularly an under-recognition of the degree of NRTI cross-resistance, and lack of treatment options for patients in whom several regimens have failed. Despite the limitations of these trial results, the clinical value of drug resistance testing is recognized and it is now considered standard-of-care in the management of treatment failure.[145] Data are not yet available on which method or type of resistance testing is superior in any given clinical setting. Resistance testing information can provide guidance when selecting which drugs to exclude or include in a new regimen. Testing should be performed when the selective pressure of the failing regimen is still present because resistance may not be detected following withdrawal of the drugs.[122] However, resistance mutations archived at the cell level may persist, with potential to rapidly reemerge if the failing regimen is reintroduced. In treatment-naive persons, drug resistance testing should be strongly considered in those who may have been infected with a resistant viral strain, particularly those with more recent infection, or when the initial response is suboptimal in the face of excellent drug adherence.[154]

Drug Concentration Monitoring

Adjusting doses of a drug to maintain a desired plasma level is common with some drugs and has been suggested for antiretroviral drugs.[155] This may be more practical with some classes of antiretroviral drugs than others. The NRTIs are especially problematic, because they require intracellular activation and because intracellular concentrations are more difficult to measure than plasma levels. Additionally, drug concentration data are most meaningful in the context of the phenotypic susceptibility of the patient's viral strain, which can be determined only in the setting of detectable viral loads.

The drug trough concentration ideally should not fall below the level necessary to control HIV replication, and the peak concentration should be below the range at which toxic effects would be expected. Composite data on the C_{min}, C_{max}, and area under the concentration curve (AUC) are generally known and available in the prescribing information for most available drugs, as is the drug concentration necessary in vitro to suppress the replication of wild-type HIV. However, there is substantial interpatient and intrapatient variability in pharmacokinetics, and suppression may be impossible if resistance has emerged. Adding yet more complexity are the different methods of determining suppression thresholds (eg, using IC_{90} or IC_{50}) and the effect of protein binding and how this is accounted for in the data reported. Data on the effect of C_{max}, AUC, or the shape of the drug-decay curve on drug toxicity or effect may be even less firm.

If monitoring of drug levels is considered, practical issues must be addressed, including adherence problems and assay availability, reliability, and cost. Possible causes of variations in drug levels must be considered, including drug-drug interactions with prescription, over-the-counter, alternative, or recreational drugs, and malabsorption due to coincident gastrointestinal disease or food effects. Finally, drug steady-state should have been reached before concentrations are measured.

Drug-concentration monitoring may be of particular value in cases of treatment failure (eg, initial or subsequent therapy), or when salvage therapy with a ritonavir-enhanced PI–based regimen has been initiated, especially if other drugs with known pharmacological interactions, such as efavirenz, are also prescribed (drug resistance testing should also be considered).

Drug concentration monitoring is commercially available in some areas. However, it is difficult to make clear recommendations, because the therapeutic range of plasma concentrations is not known for most drugs. Moreover, few studies have demonstrated the clinical usefulness of drug-concentration monitoring.[156] Thus, decisions about adjusting doses of antiretroviral drugs based on level determinations need to be individualized until more data are available.

ESTABLISHED INFECTION: CHANGING THERAPY

Changing Drugs Because of Incomplete Adherence, Adverse Effects, or Intolerance

In the absence of virological or immunologic failure, a regimen may pose problems with adherence, intolerance, or cumulative (long-term) toxic effects. As long as the antiviral activity of the overall regimen is maintained, exchanging individual components of the regimen is acceptable. Examples of such substitutions are a change of stavudine for zidovudine or nevirapine for efavirenz, or substitution of low-dose ritonavir-boosted PIs for single PI components of a regimen.

Substituting individual antiretroviral agents is frequently indicated because of drug-specific toxic effects. In clinical settings in which the offending agent cannot be easily determined, or in which there are significant safety concerns, treatment should be completely interrupted so that acute adverse effects can resolve while alternative regimens are considered. Among patients with serum lipid abnormalities and lipodystrophy, abacavir or nevirapine can be substituted for the PI component.[53] Serum lipid abnormalities improve with these changes but improvements in body composition abnormalities have not been consistently documented in studies reported to date.[53] More studies and longer patient follow-up are needed. When a change in a drug class is planned, it is preferable to do so in the setting of successful virological suppression.

Changing Therapy Because of Treatment Failure

The definition of "treatment failure" (a term that subsumes virological, immunologic, or clinical failure) depends on the clinical setting and mirrors the objective of ongoing therapy at a given time in the patient's treatment course. The duration of response is predicted by level of viral suppression obtained while receiving therapy within 8 weeks.[138,157-159] In the case of the first or second regimen, when virus is wild type

or harbors few resistance mutations, maintaining an undetectable viral load is an achievable goal of therapy; in this setting, treatment failure is best defined as inability to achieve a viral load below assay detection limits (eg, <50 copies/mL) or as any sustained return of the viral load to above the target value (eg, >400 copies/mL). With increasing rounds of treatment failure, the level and spectrum of virus resistance may increase, and it may become more difficult to construct an active combination. In patients for whom several regimens have failed, the virus may become multiply resistant, with fewer than 3 active drugs being available, and the objective of achieving stable undetectable viral load with conventional regimens may be unrealistic. Problems with toxicity may further restrict the number of available drugs. The goal of therapy in this setting is primarily to prevent clinical progression, and failure can be defined as a deterioration of the CD4 cell count or the occurrence of a serious opportunistic infection.

First or Second Failure. Treatment failure occurs within the first year of therapy in a substantial proportion of treatment-naive patients.[160,161] A lower, but definite, rate of treatment failure in successive years has been reported with nearly all regimens.[14,111] Thus, failure should be anticipated as part of the long-term strategy of antiretroviral treatment. In the case of confirmed treatment failure, an intervention should be considered promptly in order to minimize emergence of cumulative drug resistance and cross-resistance that will limit availability of alternative options.[162] However, treatment failure is not always associated with viral resistance, particularly during initial viral rebound or if virus remains detectable at a low level after several months of therapy.[96] In such circumstances a thorough assessment of adherence, dietary requirements, drug-drug interactions, and bioavailability is the first step. In situations where there is no evidence of resistance or adherence issues, adding a new drug or drugs (ie, regimen intensification) may be considered. However, since intensification may add to the complexity of the treatment regimen, such an approach could aggravate problems with adherence. Some drugs, particularly the NNRTIs and lamivudine, generally should not be used alone as intensification agents because of risk of single-step, high-level resistance. Intensifying with ritonavir as a pharmacological enhancer of another PI may be effective in the short term in patients for whom a regimen with a single PI is failing.[152] Addition of abacavir or tenofovir disoproxil fumarate may also be of use in this setting.[163]

When a decision is made to change therapy because of sustained virological failure, the new regimen should be one with highest likely effectiveness, as predicted by the patient's complete drug history and the resistance test result, as well as highest likelihood of tolerability and adherence. New regimens should contain at least 2, and if possible 3, drugs deemed to be active. Virus that replicates during treatment failure may not be resistant to all of the drugs in the failing regimen.[96,152] However, latently infected lymphocytes may harbor archived virus resistant to drugs used in the past but not detected by routine resistance testing. Shared-resistance mutations conferred by an individual drug may lead to cross-resistance among drugs in the same class, complicating the choice of alternative regimens.[146,164] With currently approved NNRTIs, risk of complete NNRTI-class cross-resistance is high when an NNRTI-containing regimen fails. With PIs, intraclass cross-resistance is not so predictable. Depending on the pattern of resistance, an alternative PI (or a combination of PIs) can often be selected. With NRTIs, extent of class cross-resistance is greater than anticipated previously, and level of resistance to some drugs (eg, stavudine) is more difficult to infer from genotype or phenotype.[145] In rare circumstances, multidrug resistance to NRTIs may develop through a unique pathway of resistance (eg, the Q151M complex or a 2–amino acid insertion at codon 69).[145] Examples of possible alternative regimens (based on predicted resistance patterns) in the setting of first regimen failure are given in **TABLE 3**.[165]

Tenofovir was recently approved for treatment of HIV infection. In its active diphosphate form, the drug has a prolonged intracellular half-life, which permits once-daily dosing.[166] The drug is active against isolates containing certain NRTI-associated resistance mutations, including the Q151M complex, but has diminished activity against isolates with the T69S insertion, the K65R mutation, and those with multiple NRTI-associated mutations (NAMs), particularly M41L and L210W.[166,167] The lamivudine-associated M184V mutation enhances tenofovir's activity in vitro.[167] The signature mutation associated with this drug is K65R, but in clinical trials and animal studies, this mutation arises infrequently and is not consistently associated with loss of antiretroviral activity.[168] In phase 3 trials in antiretroviral-experienced patients with virological failure, tenofovir has produced a consistent 0.6 $\log_{10}$ decrease from baseline in viral load and modest rises in CD4 cell counts over 24 and 48 weeks or longer.[169,170] Among treatment-naive patients treated with tenofovir monotherapy for 21 days, a 1.5 $\log_{10}$ reduction in HIV RNA was observed.[171] The drug is generally well tolerated.[169,170] No serious renal dysfunction or bone density alterations have been reported to date. The available clinical trial results suggest a role for tenofovir in management of treatment-experienced patients. Results from ongoing studies will help define the role of tenofovir in management of drug-naive patients.

Multiple Failures. Treatment histories and results of resistance testing may indicate that 2 or fewer active drugs are available for therapy in patients in whom numerous regimens have failed.

Evidence of low rates of clinical progression in such patients, who continue antiretroviral therapy despite viral replication and presence of resistance, argues for continuing treatment in the face of virological failure.[172] Some virus with multidrug-

resistance mutations has reduced replicative capacity, or fitness, relative to wild-type virus.[122,173,174] Stabilization of CD4 cell numbers and absence of clinical progression have been demonstrated when viral load is sustained at a level 3-fold (0.5 $\log_{10}$) below the patient's natural set point (pretreatment value).[172,175] Conversely, when all drugs in a regimen are stopped there may be an apparent reversion to wild-type virus within 8 to 12 weeks, associated with a rapid increase in viral load and marked decrease in CD4 cell count.[122,176] Although there is a risk of accumulating additional resistance mutations, continuing drug regimens that maintain selective pressure on the virus is preferable to discontinuing all antiretroviral therapy, especially in settings in which the CD4 cell counts are maintained despite a rebound in viral replication.

In cases in which a change in the therapy cannot be delayed, adding 1 new drug (eg, a drug available through expanded access) may not result in a profound and durable effect, and the best therapy should be selected, based on treatment history, tolerance, and resistance testing. The regimen may include drugs recycled from previous, failed regimens. Multidrug rescue therapy (6 or more drugs, also called "megaHAART") in this setting may exhibit a substantial degree of antiretroviral activity.[177,178] However, this approach may lead to toxic effects and problems with adherence, adverse drug-drug interactions, and increased cost. Moreover, the effect on CD4 cell count is not entirely predictable.[179]

ADJUVANT THERAPY TO ANTIRETROVIRAL DRUGS

The concept of manipulating the immune response for host benefit has received increased emphasis. Approaches include attempts to augment (eg, interleukin 2[180-184]) or dampen (eg, cyclosporin A, corticosteroids, hydroxyurea, and mycophenolic acid[185,186]) the immune response generally, and attempts designed to stimulate (treatment interruption and "therapeutic" vaccination[187-189]) relevant HIV-specific immune effector responses. At this point, however, insufficient clinical data exist to recommend these approaches outside the setting of clinical trials. In addition, in the case of hydroxyurea, significant toxicities have emerged that have dampened enthusiasm for this agent.[190]

SUMMARY

The future of antiretroviral therapy rests with the development of new drugs that will result in simpler, more effective, and less toxic regimens along with development of an improved understanding of innate immune system responses and novel approaches to exploit these responses. Several new agents are currently in development, derived from current drug classes (eg, the NRTIs amdoxovir and emtricitabine, the NNRTIs DPC-083 and TMC-125, and the PIs atazanavir and tipranavir) and new drug classes, including entry inhibitors (eg, enfuvirtide) and integrase inhibitors.

Table 3. Possible Regimens Following Initial Antiretroviral Regimen Failure, Based on Predicted Resistance Patterns Associated With Early Virological Failure*

Initial Regimen	Predicted Early Resistance Pattern†	Possible Interventions
	Generally Recommended	
NNRTI-sparing regimen PI (with/without low-dose ritonavir) plus 2 NRTIs	M184V‡ if regimen includes lamivudine	Revise/strengthen NRTI/NtRTI component Ritonavir boost PI component, if not part of initial regimen Change to NNRTI-based regimen
PI-sparing regimen NNRTI plus 2 NRTIs	M184V‡ with/without NNRTI-associated mutation, if regimen includes lamivudine	Revise/strengthen NRTI/NtRTI component Change to PI-based regimen if NNRTI resistance present
PI-Sparing/NNRTI-sparing regimen 3 NRTIs (including abacavir)	M184V‡ if regimen includes lamivudine	Change to PI- or NNRTI-based regimen with revision or strengthening of NRTI component or consider adding NtRTI
	Special Circumstances	
PI (with/without low-dose ritonavir) plus NNRTI plus 1 or 2 NRTIs	M184V‡ with/without NNRTI-associated mutation, if regimen includes lamivudine	Revise/strengthen NRTI component Ritonavir boost PI component if not part of initial regimen Eliminate NNRTI if associated mutation present
	Under Investigation	
NRTI-sparing regimen PI (with low-dose ritonavir) plus NNRTI	NNRTI-associated mutation	Eliminate NNRTI and add 2 NRTIs or consider adding NtRTI

*NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; and NtRTI, nucleotide reverse transcriptase inhibitor.
†The likely drug resistance patterns are listed for illustrative purposes assuming virological failure is detected early. Drug-resistance testing is recommended to determine the actual genotype or phenotype profile of the patient's viral strain.
‡The M184V mutation confers high-level resistance (500- to 1000-fold decrease in susceptibility) to lamivudine and low-level resistance (2- to 4-fold decrease in susceptibility) to abacavir.[165]

Potential advantages of these drugs include once-daily dosing, smaller pill size, lower incidence of adverse effects, new viral targets, and activity against virus that is resistant to other drugs in the respective classes. The benefits of current and future agents will continue to be felt by HIV-infected persons in the developed world. Extending these benefits to those living with HIV in the developing world is a challenge that needs to be met.

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