Consensus Statement ▬

Antiretroviral Therapy for HIV Infection in 1996

Recommendations of an International Panel

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Objective.—To provide clinical recommendations for antiretroviral therapy for human immunodeficiency virus (HIV) disease with currently (mid 1996) available drugs. When to start therapy, what to start with, when to change, and what to change to were addressed.

Participants.—A 13-member panel representing international expertise in antiretroviral research and HIV patient care was selected by the International AIDS Society–USA.

Evidence.—Available clinical and basic science data, including phase 3 controlled trials, clinical endpoint data, virologic and immunologic endpoint data, interim analyses, studies of HIV pathophysiology, and expert opinions of panel members were considered. Recommendations were limited to drugs available in mid 1996.

Process.—For each question posed, 1 or more member(s) reviewed and presented available data. Recommendations were determined by group consensus (January 1996); revisions as warranted by new data were incorporated by group consensus (February-May 1996).

Conclusions.—Recent data on HIV pathogenesis, methods to determine plasma HIV RNA, clinical trial data, and availability of new drugs point to the need for new approaches to treatment. Therapy is recommended based on CD4+ cell count, plasma HIV RNA level, or clinical status. Preferred initial drug regimens include nucleoside combinations; at present protease inhibitors are probably best reserved for patients at higher progression risk. For treatment failure or drug intolerance, subsequent regimen considerations include reasons for changing therapy, available drug options, disease stage, underlying conditions, and concomitant medication(s). Therapy for primary (acute) infection, high-risk exposures to HIV, and maternal-to-fetal transmission are also addressed. Therapeutic approaches need to be updated as new data continue to emerge.

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IMPORTANT ADVANCES in understanding the biology and treatment of human immunodeficiency virus (HIV) infection have occurred during the past 18 months. As a result, new scientifically sound approaches to therapy have been developed that offer new options for persons with HIV infection. The relevant recent advances fall into 4 major categories: (1) a better understanding of the replication kinetics of HIV throughout all stages of disease; (2) the development of assays to determine the viral load in individual patients; (3) the availability of several new effective drugs; and (4) the demonstration that combination therapy is more effective than zidovudine monotherapy.

In light of these advances, the recommendations of earlier state-of-the-art guidelines[1,2] are no longer applicable to clinical decision making in 1996. Therefore, an international panel of clinical investigators experienced in HIV patient care was selected and convened by the International AIDS Society–USA to develop current recommendations for the clinical management of HIV-infected individuals.

The panel addressed 4 central questions about antiretroviral therapy: when to initiate therapy, which types of drugs to use, when to change therapy, and which types of drugs to use when a change in therapy is indicated. In addition, the treatment of primary HIV infection, prevention of vertical transmission, and postexposure prophylaxis were addressed. The recommendations are not solely based on the results of controlled clinical trials with well-defined clinical endpoints. Developing clinical guidelines in the HIV field at this time requires an approach firmly anchored in data from controlled, double-blind clinical trials when available, but must also include information from trials in progress and available virologic and immunologic endpoint data, as well as extrapolations from studies of the pathophysiology of HIV infection. Clinical decisions must be made for best use of up to 8 available antiretroviral drugs, at a time when long-term studies with clinical endpoints have been completed for only a few possible combinations.

The recommendations herein reflect the panel's agreement on the importance of plasma HIV RNA measurements for predicting risk of clinical progression as well as of the recent demonstration from clinical trials of combination therapies that reductions in plasma HIV RNA

levels are associated with increased survival and decreased progression to AIDS. The recommendations do not provide precise algorithms for treatment of specific clinical situations, because available data do not define a single first-line regimen for any given indication. Acknowledging the paucity of clinical trial experience with some drug combinations and with all of the newly available protease inhibitors, the goal of the recommendations is to provide enough information to permit rational decisions for regimens and strategies in mid 1996.

INITIATING ANTIRETROVIRAL THERAPY

Background

Recent data have shed important light on the virologic and immunologic dynamics of HIV infection (reviewed in reference 3). Early infection of lymphoid tissue,[4,5] with continuous high-level viral replication throughout the course of the disease, is well documented.[6-8] Half of the virus population in plasma is turned over within hours, which translates to billions of virions produced and destroyed daily.[7,9] Several billion CD4 cells are likewise produced and destroyed each day.

The rate of virus replication stabilizes after primary infection at a particular level or "set point" in each individual. This level appears to be between 10^2 and 10^6 HIV RNA copies/mL of plasma and remains relatively stable in asymptomatic patients over months and possibly years.[10] Although it is convenient to measure viral RNA in plasma, it should be emphasized that these RNA levels are an indirect reflection of the number of productively infected cells in the body as a whole, and that most viral replication occurs in extravascular fixed lymphoid tissues. It is this viral replication in lymphoid tissues rather than circulating virus per se that is mechanistically linked to the progressive immunologic depletion that characterizes the illness. Although there appears to be a proportionality between plasma viral RNA and the amount of virus in fixed lymphoid tissues, the total amount of virus in the body cannot be directly calculated from the plasma viral RNA level. The set point is strongly associated with rate of disease progression and time to death, with a continuum of increased risk with increased plasma HIV RNA level. At one extreme of this continuum, a small proportion of subjects with very long-standing HIV infection have low HIV RNA levels and near-normal CD4 cell counts and appear to have a particularly prolonged course. At the other extreme, those with

high levels of plasma viremia (>50 000-100 000 HIV RNA copies/mL) are at a greatly increased risk of clinical progression.

Several observational studies and treatment trials have confirmed this gradient of risk according to baseline plasma HIV RNA level.[11-14] With remarkable agreement between 2 recent studies, subjects in the lowest quartile (the 25% of subjects with the lowest viral load; <5000 HIV RNA copies/mL of plasma) had the lowest risk of progression to clinical acquired immunodeficiency syndrome (AIDS) and death. Subjects with a plasma virus level of more than about 30 000 to 50 000 HIV RNA copies/mL (the highest quartile) were at the greatest risk of progression.[11,12]

HIV RNA levels appear to be more predictive of progression than CD4 counts, particularly in asymptomatic patients with cell counts higher than 0.350×10^9/L ($350/\mu$L).[11,15] The CD4 cell numbers may be difficult to interpret because the number at any point in time is only a partial indicator of the risk of AIDS.[16] The onset of HIV-related symptoms is a strong predictor of further progression to serious opportunistic diseases.

Until recently, entry criteria for most clinical trials of antiretroviral drugs have centered on pretreatment symptom status, prior treatment history, and entry CD4 cell count. Overall, zidovudine monotherapy was shown to be effective in advanced symptomatic disease, in mildly symptomatic disease, and in asymptomatic patients with CD4 cell counts less than 0.500×10^9/L.[17-20] In patients with CD4 cell counts higher than 0.500×10^9/L, zidovudine monotherapy reduced CD4 cell loss but had no significant effect on clinical progression to AIDS or on survival compared with initiation of the drug at CD4 cell count at or below 0.500×10^9/L.[21]

More recently, plasma HIV RNA assays have permitted smaller and more efficient trial designs using viral load measurements in addition to or instead of clinical and CD4+ cell endpoints. Because of the important new insights gained from the use of these assays, strategies for earlier treatment with more potent combination antiretroviral regimens in asymptomatic disease are being considered.[11,12,22-28]

In addition to the usefulness in assessing prognosis and guiding the initiation of therapy, HIV RNA levels are of potential value in assessing response to therapy (see next section). Reductions of HIV RNA titer generally occur within 4 weeks of starting or changing treatment. Several of the more potent combinations of antiretroviral drugs are

capable of inducing such profound reductions in viral replication that virus is no longer detectable in plasma with currently available techniques. Although studies of the relationship between changes in viral RNA in plasma and changes in the levels of virus in fixed lymphoid tissues are fragmentary, those that have been completed suggest that changes in the plasma compartment are an indirect reflection of events in fixed lymphoid tissues.[29,30] A reduction in plasma viral RNA to levels that are below those detectable by current techniques does not necessarily reflect complete suppression of viral replication. As an estimated 10^9 to 10^{10} virions are produced daily, it is highly likely that HIV-1 replication continues in lymphoid tissues following a reduction in plasma viral RNA by 2 to 4 $\log_{10}$, albeit at a significantly lower rate.[6] Even at these lower replication rates it would be expected that viral variants with reduced susceptibility to antiretroviral drugs will evolve over time. In that viral variation begins with the first cycles of replication during primary infection, as HIV-1 infection proceeds a subpopulation of viral variants that is resistant to antiretroviral drugs evolves, even in the absence of selective pressure. The prevalence of such mutants in the population of virus prior to the initiation of antiretroviral therapy is a function of the number of prior rounds of viral replication, the mutation rate, and the selective advantage (fitness) possessed by wild-type virus over variants that have incorporated mutations conferring drug resistance.[31,32] Such considerations add further support to the concept that earlier initiation of therapy would be expected to result in a more durable response than would be expected in later stages of illness when a broader array of drug-resistant mutants would be expected to be present. Reductions in plasma viremia correlate with increased CD4 cell numbers and AIDS-free survival.[12,15] Treatments that achieve a greater and more durable suppression of HIV replication are assumed to be of greater clinical benefit. However, the magnitude and durability of the clinical benefits associated with plasma viral RNA suppression to undetectable levels have not been established.

Antiretroviral-Naive Patients.—Several trials have shown improvement based on laboratory indices or clinical benefits of combinations of 2 nucleoside analogues for initial therapy in HIV infection (Table 1). Three trials compared combination therapy with zidovudine and didanosine or zidovudine and zalcitabine with monotherapy regimens. In the US AIDS Clinical Trials Group

Table 1.—Results of Selected Recent Controlled Clinical Trials of Nucleoside Analogues: Studies With 250 Patients or More Observed for 48 Weeks or More

Regimen*	No. of Studies (References)	Approximate No. of Patients	Maximum CD4+ Cell Count Increase, ×10⁹/L†	Maximum HIV RNA Reduction, log₁₀ Copies/mL†
Trials of initial therapy in antiretroviral-naive subjects				
Zidovudine/didanosine	3 (12, 27, 33-35)	1000	0.085	1.4
Zidovudine/zalcitabine	3 (12, 27, 33-35)	1000	0.085	1.1
Didanosine	1 (12, 33)	250	0.040	0.8
Zidovudine/lamivudine	2 (24, 36, 107)	300	0.085	1.7
Trials in antiretroviral-experienced patients‡				
Zidovudine/didanosine	3 (12, 33-35, 108)	1000	0.040	1.1
Zidovudine/zalcitabine	3 (12, 22, 33-35)	800	0.020	0.9
Didanosine	1 (12, 33)	350	0.035	0.7
Zidovudine/lamivudine	2 (41, 56, 109)	275	0.032	1.5

*Each of these regimens except zidovudine/lamivudine has been shown to be superior to zidovudine monotherapy in delaying disease progression or death. Comparable data on the effect of zidovudine/lamivudine on clinical outcome are pending, but not yet available.
†For regimens evaluated in more than 1 trial, the maximum value is the highest mean peak value reported. HIV indicates human immunodeficiency virus.
‡The populations in the studies of antiretroviral-experienced patients vary considerably in terms of stage of disease and extent of pretreatment at entry.

(ACTG) 175 study, previously untreated patients with CD4+ cell counts of 0.200 to 0.500×10⁹/L at entry randomized to combination therapy had sustained clinical benefits and plasma HIV RNA and CD4+ count improvements[12,33]; very similar results were obtained in the European-Australian trial, Delta 1, in patients with CD4+ cell counts of less than 0.350×10⁹/L at entry.[34,35] In ACTG 175, didanosine monotherapy was as effective as the combinations and was superior to zidovudine monotherapy; didanosine alone was not evaluated in the Delta 1 study. In other studies, initial combination treatment with zidovudine and lamivudine reduced plasma HIV RNA levels and raised CD4+ cell counts more than either drug alone[24,36] for longer than 76 weeks in some patients. These trials were not powered to detect differences in rates of clinical endpoints.

There are limited data on other initial nucleoside analogue-containing regimens that do not include zidovudine. In a small study of asymptomatic patients with CD4+ cell counts of less than 0.500×10⁹/L, the combination of stavudine and didanosine had laboratory effects comparable to any of the other 2-drug combinations studied to date and modest toxic effects.[37] The combination of stavudine and lamivudine may have similar antiretroviral potency and tolerability, but no data are currently available on the combination. Stavudine monotherapy is also being investigated for initial therapy, and preliminary data indicate antiretroviral activity comparable to zidovudine.[38]

Antiretroviral-Experienced Patients.—Results of some clinical trials in antiretroviral-experienced populations are considered because they provide insight into potential regimens for initial treatment. The US Community Programs for Clinical Research on AIDS (CPCRA) 007 trial compared combination therapy (zidovudine/didanosine or zidovudine/zalcitabine) with zidovudine monotherapy in patients with CD4+ cell counts less than 0.200×10⁹/L or with AIDS at entry.[39] Overall, there were CD4+ cell count increases but no clinical benefit with combination therapies. However, most patients had prior zidovudine therapy (median, 12 months) and the risk of disease progression or death increased proportionally to the duration of prior zidovudine therapy for both combinations. In the subset of antiretroviral-naive patients or those with less than 12 months of prior therapy, clinical progression or death was reduced in the zidovudine/didanosine group.

Combinations of nucleoside analogues with or without protease inhibitors appear to have more potent antiretroviral activity than monotherapy and may also delay or prevent the emergence of drug resistance. Several recent trials of protease inhibitor–containing combinations have been reported. In patients with moderately advanced disease, there were more substantial effects on laboratory markers with the combination of zidovudine, zalcitabine, and saquinavir than with the combination of zidovudine and saquinavir or the combination of zidovudine and zalcitabine.[22] In 1 large phase 3 study, patients with CD4+ cell counts of 0.050 to 0.300×10⁹/L and at least 16 weeks of prior zidovudine therapy, the combination of saquinavir and zalcitabine was associated with significantly better clinical ($P=.002$) and survival ($P=.002$) outcomes than either saquinavir or zalcitabine alone.[40] These effects were, however, less striking than those seen subsequently with better absorbed protease inhibitors. In a small study, the combination of zidovudine, lamivudine, and indinavir resulted in a greater than 2.5 log₁₀ HIV RNA reduction at 16 weeks; more than 90% of those patients had reductions to fewer than 500 HIV RNA copies/mL at 6 months.[41] The triple-drug combination was as well

tolerated as indinavir alone or zidovudine/lamivudine. The combination of zidovudine, zalcitabine, and ritonavir exhibited antiretroviral activity comparable to zidovudine, lamivudine, and indinavir.[42] In a large trial in patients with very advanced HIV disease (median CD4+ cell count of 0.018×10⁹/L), the addition of ritonavir to an existing regimen (including no current therapy) reduced progression to AIDS and mortality by approximately 50%.[43,44] As yet, however, there are very few data from long-term (≥52 weeks), large (≥250 patients) controlled clinical trials of any protease inhibitors.

Lead compounds in the nonnucleoside reverse transcriptase inhibitor (NNRTI) class, nevirapine, delavirdine, and loviride, are extremely potent in vitro, but are associated with rapid development of viral resistance. Efforts are continuing to reduce the clinical impact of viral resistance by using higher drug doses and combination therapy with nucleoside analogues and protease inhibitors and evaluating these drug combinations for initial therapy.

When to Initiate Therapy

Ideally, therapy of HIV infection should be initiated before irreversible immunologic damage has occurred. The decision of when to initiate therapy should be based on the assessment of disease progression risk. Natural history studies and treatment trials demonstrate a continuum of increased risk with higher viral load and lower CD4+ cell count. As such, the experts differ somewhat with regard to the precise trigger point for recommending therapy (Table 2).

Clinical trial data support the initiation of therapy in patients with CD4+ cell counts below 0.500×10⁹/L (or a CD4+ percentage of <25). Some experts would defer therapy in a subset of patients with stable CD4+ cell counts between

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Status	Recommendation
Symptomatic HIV disease*	Therapy recommended for all patients
Asymptomatic, CD4- cell count <0.500×10⁹/L	Therapy recommended†
Asymptomatic, CD4- cell count >0.500×10⁹/L	Therapy recommended for patients with >30 000-50 000 HIV RNA copies/mL or rapidly declining CD4- cell counts
	Therapy should be considered for patients with >5000-10 000 HIV RNA copies/mL

*Symptomatic human immunodeficiency virus (HIV) disease includes symptoms such as recurrent mucosal candidiasis, oral hairy leukoplakia, and chronic and un-explained fever, night sweats, and weight loss.
†Some would defer therapy in a subset of patients with stable CD4- cell counts between 0.350 and 0.500 × 10⁹/L and plasma HIV RNA levels consistently below 5000-10000 copies/mL.

0.350 and 0.500×10⁹/L (eg, counts that remain at the same level for 18 to 36 months) in whom plasma HIV RNA levels are consistently less than 5000 to 10 000 HIV RNA copies/mL.

Available clinical trial results do not define the optimal treatment strategy for asymptomatic patients with CD4+ cell counts above 0.500×10⁹/L. In such patients, treatment is recommended for those with more than 30 000 to 50 000 HIV RNA copies/mL or with rapidly declining CD4+ cell counts (ie, a greater than 0.300×10⁹/L loss over 12 to 18 months), based on the very high progression risk. Treatment should be considered for patients with HIV RNA levels higher than 5000 to 10 000 copies/mL based on the high progression risk. However, any decision to initiate therapy at CD4+ cell counts above 0.500×10⁹/L must be tempered by the fact that there are no available clinical data to support treatment at this stage of HIV disease, and that such earlier therapy carries with it potential problems related to long-term toxicity, tolerance, acceptance, expense, and the possible induction of drug-resistant virus.

Antiretroviral therapy should be initiated in all patients with symptomatic HIV disease (eg, recurrent mucosal candidiasis; oral hairy leukoplakia; chronic or otherwise unexplained fever, night sweats, or weight loss).

Initial Antiretroviral Regimens

A central question in the choice of an initial antiretroviral regimen is whether to use the most potent antiretroviral therapy available first in all patients or to reserve such therapy for patients with a higher pretreatment progression risk or for those progressing after initial therapy has been instituted. At this time, both approaches are defensible. Based on current virologic and immunologic data, the most potent treatment regimen at this time would probably include 2 nucleoside analogues and a potent protease inhibitor; however, experience with protease inhibitors as initial therapy and in early HIV disease is still limited. Until longer-term clinical trial data from initial regimens with protease inhibitors are available, most patients in whom therapy is indicated should probably begin with 1 of the nucleoside analogue-containing regimens described below (Table 3).

The nucleoside analogue combinations with the most demonstrated clinical benefits are zidovudine/didanosine and zidovudine/zalcitabine (Table 1). Zidovudine/lamivudine may be better tolerated and appears to have comparable antiretroviral potency, but supporting clinical endpoint data are not now available. Also, there is some concern that initial lamivudine therapy with resulting resistance mutations at reverse transcriptase codon 184 may impair later response to didanosine or zalcitabine, should they be required.

Although emerging data support combination therapy, didanosine monotherapy is also a reasonable option,[12,33] particularly for patients who cannot tolerate or who refuse zidovudine. This approach may allow the possibility of adding zidovudine at a later time or switching to zidovudine/zalcitabine or zidovudine/lamivudine, although there are no published data regarding the efficacy of these regimens in patients previously treated with didanosine monotherapy.

Initial therapy with other non–zidovudine-containing combinations are less well supported by clinical trial data. Stavudine/didanosine has antiretroviral potency that appears comparable to other 2-drug combinations[37]; careful monitoring is clearly indicated for neurotoxicity, especially in more advanced disease. Stavudine/lamivudine is well tolerated, particularly for patients with limited bone marrow reserve who are poor candidates for zidovudine-containing regimens. However, no formal evaluation of the pharmacokinetics, safety, or activity of the combination has been completed. Stavudine monotherapy is also well tolerated, but available information does not permit adequate comparisons with other initial monotherapies (zidovudine or didanosine). Zalcitabine and lamivudine are not satisfactory single-drug therapies.

As noted, it may be reasonable to include a protease inhibitor in the initial regimen for any patient in whom therapy is indicated, particularly for patients at higher risk for progression. In this strategy, a protease inhibitor could be added for symptomatic patients, patients with lower or rapidly falling CD4· cell counts, and those with high plasma HIV RNA levels. The choice of a protease inhibitor should be made on the basis of efficacy and potency, safety and tolerability, durability of antiviral effects, drug resistance patterns, the potential for limiting future treatment options, and cost. Saquinavir, the first approved protease inhibitor, is well tolerated but has limited bioavailability and thus potency in its currently available formulation. A new formulation with improved bioavailability is under study. Indinavir is very potent and well tolerated. Toxic effects include benign hyperbilirubinemia and a 3% to 4% rate of nephrolithiasis (stones are primarily composed of precipitated indinavir). Ritonavir is comparable in potency to indinavir; it has more frequent adverse effects including gastrointestinal disturbance (20% to 25% of patients), hepatotoxicity, headache, and transient circumoral paresthesia. Ritonavir is a particularly efficient inhibitor of the hepatic enzyme cytochrome P450, which complicates its use with other drugs metabolized by this pathway. This may be particularly difficult in patients with advanced HIV disease in whom 1 or more of these drugs are commonly required.

The choice of initial therapy, including use of nucleosides and protease inhibitors, may be guided by emerging data on cross-resistance between drugs.[45] In the case of nucleosides, cross-resistance among lamivudine, didanosine, and zalcitabine based on codon 184 mutations provides an example of these concerns. The frequency of selection for viruses that are cross-resistant in vitro to some protease inhibitors suggest that an initial drug may limit future options for additional or alternative protease inhibitors.[46] Limited data from in vitro and sequential treatment studies support the hypothesis that ritonavir and indinavir select multiple mutations that often confer cross-resistance between these drugs. The mutations most commonly selected by saquinavir therapy in vivo are different and less numerous and may not confer cross-resistance in vitro.[45] However, some of the saquinavir-selected mutations have also been seen in subjects receiving indinavir and ritonavir, and the clinical consequences of initiating one protease inhibitor with respect to possible future benefits of another have not yet been fully defined. The clinical correlates of protease inhibitor resistance and cross-resistance will only be defined by careful analysis of current and future studies. It is important to maintain continuous drug administration at the optimal dosage level with all protease inhibitors, as dose re-

Table 3.—Recommendations for Initial Therapy Regimens

Zidovudine/didanosine, or zidovudine/zalcitabine, or zidovudine/lamivudine, or didanosine monotherapy*	If a protease inhibitor is added to a nucleoside analogue-containing regimen, the choice of protease inhibitor should be based primarily on antiretroviral potency and secondarily on other considerations as described in the text†

*Didanosine monotherapy may be less effective as initial therapy in patients with more advanced human immunodeficiency virus (HIV) disease. Other possible non–zidovudine-containing regimens include didanosine/stavudine, stavudine/lamivudine, and stavudine monotherapy, although these regimens are less well studied.

†Antiretroviral potency refers to plasma HIV RNA and CD4+ cell count responses associated with these drugs at approved doses and with currently available formulations.

duction will contribute to the development of resistance to these drugs. When drug toxicity develops it is generally better to stop the protease inhibitor drug than to reduce its dose.

CHANGING ANTIRETROVIRAL THERAPY

Reasons for Changing Therapy

The initial antiretroviral regimen is of critical importance; however, few patients will remain on that treatment for prolonged periods of time. In general, there are 3 primary reasons for considering a change in antiretroviral therapy:

1. Treatment failure. Increased viral replication, due at least in part to the emergence of drug-resistant viral variants, is directly linked to immunologic and clinical progression. Treatment failure is indicated by increases in viral load (eg, a return toward or within 0.3 to 0.5 log$_{10}$ of pretreatment plasma HIV RNA levels), decreases in CD4+ cell count or percentage, or clinical progression. Ideally the patient should be monitored frequently enough that the decision to change the regimen can be made before symptomatic disease progression occurs.

Plasma HIV RNA assays have provided precise and compelling data on the relative magnitude and durability of effects of antiretroviral regimens. These data underscore the potential of plasma viral load levels, in conjunction with CD4+ cell counts, for guiding treatment decisions. Preliminary guidelines are available for using plasma HIV RNA levels in individual patient management.[47] If used, plasma HIV RNA level should be measured 3 to 4 weeks after initiating or changing therapy, and then periodically on the same schedule as CD4+ cell counts (eg, every 3 to 6 months). The minimum reduction in HIV RNA titer indicative of antiretroviral activity is 0.5 log$_{10}$ or more (about 3-fold) from pretreatment value (based on intra-assay variability of about 0.2 log$_{10}$ and biologic variation of about 0.3 log$_{10}$). The HIV RNA levels measured within about 1 month after immunizations or active intercurrent illnesses may show substantial but transient elevations associated with these events, which will resolve without alteration in therapy.[48-50]

CD4+ cell enumeration has been ex-

tensively used to guide treatment decisions. As with plasma HIV RNA measurements, it is not possible to strictly define CD4+ cell changes that definitely indicate that a change in therapy should be made. Most experts would view a return of CD4+ cell counts to pretreatment values as evidence of a loss of drug effect. Other factors, such as rate of decline of CD4+ cell count and extent to which additional treatment regimens are available, should also be considered.

The occurrence of HIV-associated clinical complications is considered evidence of treatment failure. The goal of using virologic and immunologic parameters to guide therapy is to prevent clinical disease progression, as clinical indicators of progression are, at best, insensitive and late indicators of treatment failure. Decisions to change treatment are often made relatively late, perhaps in part because of limited options and access to drugs, the general conservatism of many physicians, and the implication that altering therapy acknowledges disease progression. However, accumulating evidence suggests that earlier decisions to change therapy are more likely to have a significant impact on disease progression.[34,35,39,51-54]

2. Toxicity, intolerance, or nonadherence. Each of the available antiretroviral treatments is associated with dose-limiting toxic effects. In general, they occur more frequently in individuals with advanced disease; in addition, overlapping toxicities with other drugs are more likely to encroach on therapeutic options in patient populations with more advanced disease. Physicians and patients must maintain an open dialogue about toxic effects and adherence to drug regimens.

3. Current use of a suboptimal treatment regimen. Zidovudine monotherapy is a suboptimal regimen and treatment should be reevaluated in any patient who is receiving it.

What to Change to

Several factors must be considered in determining which drugs should be added or substituted when a decision is made to change therapy, including the primary reason for changing, prior treatment history, currently available options, stage of disease, underlying conditions

(eg, neuropathy), concomitant medications, and cost and reimbursement issues associated with the regimens. An essential consideration relates to why a change in therapy is being made. For toxicity or intolerance, finding a regimen that a patient will tolerate and be willing to take on an ongoing basis is crucial. For treatment failure, drugs with greater potency, with different mechanism(s) of action, and those without cross-resistance should be sought.

With an expanding number of available antiretroviral drugs, opportunities will arise for continuing modification of the antiretroviral regimen, and the decision to use a particularly potent therapy early in treatment should be weighed against the type of regimen that can be employed at later stages of HIV disease. As with the recommendations for initial treatment, the most appropriate regimen cannot be defined specifically for each clinical scenario. In general, a change to the most potent regimen available is recommended, based on the virologic, immunologic, and clinical characteristics of the individual patient. Table 4 provides some representative options for subsequent regimens.

Patients currently on zidovudine monotherapy should be reevaluated as to whether a more potent antiretroviral regimen (eg, adding didanosine, zalcitabine, or lamivudine to the zidovudine regimen, or switching to didanosine monotherapy) should be recommended.[12,34,35,51,53,55] In patients with advanced disease and those with extensive zidovudine experience, adding lamivudine to zidovudine or switching to another type of nucleoside analogue combination with or without a protease inhibitor may be beneficial. In patients with advanced disease, switching to zalcitabine or adding zalcitabine provides no additional benefit over zidovudine monotherapy.[39,52,56] The benefits of adding didanosine are more modest than those observed with the initial use of this combination and are less demonstrable or absent in patients with extensive zidovudine experience or advanced disease.[12,34,35,39,51,53] In such patients, new combinations of nucleoside analogues plus a protease inhibitor are appropriate.

In patients who have received a combination of 2 nucleoside analogues, such as zidovudine/didanosine, zidovudine/zalcitabine, or zidovudine/lamivudine, a change to combination therapy with at least 2 new drugs, such as 1 or 2 nucleoside analogues and a protease inhibitor (indinavir, ritonavir, saquinavir) may be appropriate. For patients for whom initial regimens included a protease inhibitor, subsequent regimens should include at least 2 new drugs; there are currently insufficient data on viral resistance pat-

Table 4.—Some Selected Options for Changing Therapy Owing to Treatment Failure or Drug Intolerance*

Initial Regimen	Subsequent Regimen Options
Treatment Failure	
Zidovudine†	Zidovudine/didanosine ± protease inhibitor
	Zidovudine/lamivudine ± protease inhibitor
	Didanosine ± protease inhibitor
	Didanosine/stavudine · protease inhibitor
Didanosine	Zidovudine/lamivudine ± protease inhibitor
	Zidovudine/didanosine/ protease inhibitor
	Stavudine/protease inhibitor
Zidovudine/didanosine	Zidovudine/lamivudine ± protease inhibitor
	Stavudine/protease inhibitor
Zidovudine/zalcitabine	Zidovudine/lamivudine ± protease inhibitor
	Stavudine/protease inhibitor
	Didanosine/protease inhibitor
Zidovudine/lamivudine	Didanosine/protease inhibitor
	Stavudine/protease inhibitor
	Didanosine/stavudine
	Lamivudine/stavudine
Drug Intolerance‡	
Zidovudine†	Didanosine
	Didanosine/stavudine
	Lamivudine/stavudine
	Stavudine
Didanosine	Zidovudine/lamivudine
	Lamivudine/stavudine
	Stavudine/protease inhibitor
Zidovudine/zalcitabine	
Intolerance to zidovudine	Didanosine
	Didanosine/protease inhibitor
	Didanosine/stavudine
	Stavudine/protease inhibitor
Intolerance to zalcitabine	Zidovudine/lamivudine ± protease inhibitor
Zidovudine/lamivudine	Didanosine/protease inhibitor
	Stavudine/protease inhibitor
	Didanosine/stavudine

*For patients whose initial regimen includes a protease inhibitor, subsequent regimens should include at least 2 new drugs chosen from among nucleoside analogues, nonnucleoside reverse transcriptase inhibitors (if available), and protease inhibitors (one should be selected for which there is likely to be little or no cross-resistance to the initial protease inhibitor).
†Considered a suboptimal regimen; all patients on zidovudine monotherapy should be reevaluated.
‡A protease inhibitor could be added to the nucleoside analogue regimens listed.

terns to be able to provide specific recommendations for additional or alternative protease inhibitors in this setting.

Considerations for Stopping Antiretroviral Therapy

Stopping antiretroviral therapy may be appropriate in patients with very advanced disease for whom there are significant toxicity and quality-of-life issues associated with continued antiretroviral therapy. Data on viral dynamics[7-9] support the need for continuous therapy with continued monitoring and reevaluation of the antiretroviral regimen. The consequences of drug withdrawal are immediately evident (within days) in terms of increases in plasma HIV RNA levels.[6,57] In light of this, efforts should be made to manage drug-related toxicity before all therapy is abandoned.

SPECIAL CONSIDERATIONS

Treatment of primary (acute) HIV infection, prophylaxis for the prevention of HIV transmission by accidental exposures, and the prevention of maternal-fetal transfer are discussed below. The latter 2 settings have been covered in detail by others.[58-60] The recommendations herein address these 3 areas with regard to recent insights into HIV pathogenesis and clinical trials of newer and more potent antiretroviral treatments.

Primary Infection

Background.—Primary HIV infection refers to the 4- to 7-week period of rapid viral replication immediately following exposure. The number of virions produced during primary infection is similar to that produced during several subsequent years of established, asymptomatic infection.[61] Roughly 30% to 60% of individuals with primary infection develop an acute syndrome characterized by fever, malaise, lymphadenopathy, pharyngitis, headache, myalgia, and sometimes rash.[62,63] Following primary infection, seroconversion and a broad HIV-1 specific immune response occur, usually within 30 to 50 days.[5]

Primary HIV infection is characterized by high plasma HIV RNA levels (10^6 to 10^7 copies/mL). Each individual seems to establish a plasma HIV RNA set point that is highly predictive of subsequent progression risk.[10,64,65] Theoretical reasons to treat during primary infection include the opportunity to intervene before the infection is fully established with the possibility of lowering the viral set point and the opportunity to intervene when the genetic diversity of HIV in each individual is more restricted.

Little information is available to guide treatment in primary HIV infection. Patients with primary infection and very recent seroconverters treated with zidovudine monotherapy (250 mg twice a day) for 6 months had slower progression to minor clinical endpoints and better CD4+ cell counts than did patients without antiretroviral treatment.[66] Reductions in plasma HIV RNA levels were more pronounced in the treated group.

Recommendations for Primary Infection.—To increase antiretroviral treatment effect and minimize or delay emergence of drug resistance (also, primary infection may have been with a drug-resistant virus), treatment of primary infection with the most potent combination therapy available seems warranted. If enrollment in a clinical trial is not possible, a combination of at least 2 nucleoside analogues is recommended (eg, zidovudine plus didanosine, zalcitabine, or lamivudine). The addition of a protease inhibitor or an NNRTI, if available, should also be considered. Preliminary investigations of 2- and 3-drug combinations are under way.

At this time, the appropriate duration of antiretroviral therapy for primary infection has not been determined. It is recommended that treatment continue for at least 6 months, the duration of the only published study.[66] Until more data are available, further treatment should be guided by clinical judgment, weighing factors including plasma HIV RNA levels and CD4+ cell counts, as well as patient acceptance, long-term drug toxicity, and cost.

Postexposure Prophylaxis

Background.—Risk of HIV transmission through occupational exposure in health care workers is approximately 0.3% from a percutaneous injury from a needle or other device.[67,68] Variables apparently related to risk of HIV transmission include volume of blood involved in the exposure (for example, 90% of transfusion recipients receiving HIV antibody–positive blood seroconvert); stage of disease and plasma HIV RNA level in the source patient; and site and mechanism of exposure.[58,67,69-71] The risk of transmission in other types of accidental exposure, ie, that among HIV laboratory workers, between sexual partners of infected individuals, and from human bites, is less well characterized.[72-74]

Zidovudine has been the predominant drug evaluated for postexposure prophylaxis. Animal data on its protective effect have been inconclusive.[75-78] There is limited experience with zidovudine prophylaxis in humans.[79-83]

In a recently reported case-control study from public health authorities in France, Great Britain, and the United States, experience with zidovudine prophylaxis was reported for 31 cases of seroconversion and for 679 controls with no seroconversion.[71] Risk factors associated with seroconversion were deep injury; visible blood on needle or device involved; procedures involving a needle placed directly into a vein or artery; and terminal illness in the source patient. Prophylaxis with zidovudine (1000 mg/d for 3 to 4 weeks) was shown to reduce risk of transmission by nearly 80%. Caution should be used in interpreting these results, however, as data were collected retrospectively; the study used case con-

trols rather than placebo controls; cases and controls were identified from different sources; and reporting or ascertainment bias is possible.

Recommendations for Post-exposure Prophylaxis.—Despite limited data, post-exposure prophylaxis is recommended in occupational and accidental situations in which there is a definite high risk for transmission.[71] Clinicians may be faced with decisions regarding prophylaxis in less well-studied exposures, such as transplantation of an HIV-positive donor organ, rape, or accidents in HIV laboratories. A level of risk per episode at least analogous to that of percutaneous needlestick injury can be assumed to exist in these settings, and a similar consideration of prophylaxis may be appropriate. Previously published guidelines on post-exposure prophylaxis recommend zidovudine, 200 mg every 4 hours for 3 days, then 100 to 200 mg every 4 hours for the next 25 days.[58] Current guidelines have been proposed by the Centers for Disease Control and Prevention Task Force.[81]

Maximal benefit of prophylaxis can be expected if therapy is begun as soon as possible after exposure (ie, within hours). It is strongly recommended that each institution develop a specific regimen and have available standard prophylaxis kits for use in occupational and nosocomial exposures. In view of the greater efficacy of combination therapy in patients with established infection and the increasing incidence of zidovudine resistance in source patients,[85-87] potent combination therapy may confer more protection than monotherapy. If possible, at least 2 drugs that have not been used in the source patient should be considered. Alternatives to zidovudine monotherapy include therapy with at least 2 nucleoside analogues (Table 3). Three or more drug regimens that include a potent protease inhibitor or an NNRTI, if available, may also be considered. Newer treatments may soon provide more choices.[23,25,26,88-92]

The specific time courses (ie, 4 to 6 weeks) for prophylaxis that have been evaluated are largely based on outmoded concepts of viral pathogenesis.[59,71] Based on the current understanding of viral replication, it may be that shorter, more intensive courses of therapy (eg, 2 weeks of triple-combination therapy) are more appropriate, but this needs further evaluation before it can be recommended.

Vertical Transmission Prophylaxis

Background.— Without antiretroviral intervention, 15% to 35% of infants born to HIV-infected mothers will acquire HIV infection.[93-96] Factors associated with increased risk of vertical transmission in-

clude the rupture of membranes for more than 4 hours and events that expose the infant to maternal blood.[60,54,97] There appears to be no threshold for maternal plasma HIV RNA levels above which transmission always occurs or below which it does not occur.[98-101]

The effectiveness of antiretroviral therapy in preventing maternal-to-fetal transmission has been demonstrated in women with CD4$^+$ cell counts above 0.200×10^9/L and little or no prior zidovudine experience.[65,89] Zidovudine therapy for the mother during the antepartum and intrapartum period and for the newborn for 6 weeks after birth reduced transmission by approximately two thirds, from 24.9% to 7.8%. Recent observational studies have also shown reduced transmission associated with zidovudine therapy.[102-104]

Recommendations for Vertical Transmission Prophylaxis.—Counseling and HIV testing should be offered to all pregnant women.[60] Perinatal prophylaxis is recommended for all HIV-infected women, as is treatment for the newborn regardless of whether the mother is treated. All women currently receiving antiretroviral therapy should continue to receive therapy during pregnancy. Following the guidelines of the AAP,[105] HIV-infected women, if local conditions permit, should be encouraged to bottle-feed their newborns as HIV can be transmitted in breast milk.[106]

There are insufficient data on efficacy, safety, or possible teratogenicity to permit recommendations of any regimen other than zidovudine for preventing vertical transmission at this time.[102]

CONCLUSIONS

More effective treatment of HIV disease is now possible, and treatment decisions have become more complex, requiring an understanding of viral pathogenesis, antiretroviral resistance patterns, and use of laboratory markers of HIV disease progression and antiretroviral efficacy. These recommendations are designed to assist clinicians in making informed decisions regarding the treatment of HIV disease and will necessarily change as new data are generated. The panel intends to update the recommendations as warranted.

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