Antiretroviral Therapy for HIV Infection in 1998

Updated Recommendations of the International AIDS Society–USA Panel

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Objective.—To provide recommendations for antiretroviral therapy based on information available in mid-1998.

Participants.—An international panel of physicians with expertise in antiretroviral research and care of patients with human immunodeficiency virus (HIV) infection, first convened by the International AIDS Society–USA in December 1995.

Evidence.—The panel reviewed available clinical and basic science study results (including phase 3 controlled trials; clinical, virologic, and immunologic end point data; data presented at research conferences; and studies of HIV pathophysiology); opinions of panel members were also considered. Recommendations were limited to drugs available in mid-1998.

Consensus Process.—Panel members monitor new clinical research reports and interim results. The full panel meets regularly to discuss how the new information may change treatment recommendations. Updated recommendations are developed through consensus of the entire panel at each stage of development.

Conclusions.—Accumulating data from clinical and pathogenesis studies continue to support early institution of potent antiretroviral therapy in patients with HIV infection. A variety of combination regimens show potency, expanding choices for initial regimens for individual patients. Plasma HIV RNA assays with increased sensitivity are important in monitoring therapeutic response; however, more data are needed to determine precisely the HIV RNA levels that define treatment failure. Long-term adverse drug effects are beginning to emerge, requiring ongoing attention. Some issues regarding optimal long-term approaches to antiretroviral management are unresolved. The increased complexity in HIV management requires ongoing monitoring of new data for optimal treatment of HIV infection.

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THE INTERNATIONAL AIDS Society–USA panel, which has previously evaluated data on antiretroviral therapy, continues to provide updates of its earlier recommendations[1,2] with the goal of providing clinicians with a practical synthesis of the therapeutic implications of human immunodeficiency virus (HIV) disease pathogenesis and clinical research. The panel consists of an international group of physicians experienced in antiretroviral drug–related research and care of patients with HIV infection. In preparing these recommendations, which were developed by consensus, available clinical and basic science data as well as expert opinion were considered. The rapidly evolving knowledge base, increasing level of sophistication of patient monitoring, and complexity of therapeutic options dictate the need for updated recommendations.

SCIENTIFIC RATIONALE FOR UPDATED RECOMMENDATIONS

Seminal observations[3,4] reported in 1995 continue to provide the pathogenetic basis for current therapeutic recommendations. The high viral turnover rate[5] and the error-prone nature of RNA virus replication support the use of potent antiretroviral combination regimens to achieve long-term control of HIV replication. Original calculations describing HIV dynamics were based on observations of the initial phase of plasma HIV-1 decline observed following antiretroviral treatment initiation.[1,2] A second phase of decline was then ob-

Table 1.—Pharmacokinetic Interactions Among Protease Inhibitors and Nonnucleoside Reverse Transcriptase Inhibitors*

	Affected Drug							
Interacting Drug	**Indinavir**	**Ritonavir**	**Saquinavir Soft Gel**	**Nelfinavir**	**Amprenavir**	**Nevirapine**	**Delaviridine**	**Efavirenz**
Indinavir	. . .	No effect (24)†	↑AUC 620%/ 800 mg; 364%/1200 mg (25, 26) Dose not established	No effect (27) ↑AUC 83%, single dose (28)	↑AUC 22%, 64% (29) No dose change	No effect (30)	No effect (31, 32)	No effect
Ritonavir	↑AUC 480% (24)†	. . .	↑AUC 121% (26)†	↑AUC 152% (28)†	Pending	No effect (30)	No effect (31-33)	↑AUC 21%
Saquinavir soft gel	Pending	No effect (26)	. . .	↑AUC 18% (34)†	Pending	No effect (35)	Pending	↓AUC 10%
Nelfinavir	No effect (27) ↑AUC 51%, single dose (28)	No effect (28)	↑AUC 392% (34)†	. . .	Pending	No effect (36)	↓AUC 40% (37) Dose not established	No effect (38, 39)
Amprenavir	No effect (29)	Pending	Pending	Pending	. . .	Pending	Pending	↑AUC 15% (29)
Nevirapine	↓AUC 28% (30)	No effect (30)	↓AUC 24% of HGC‡ (26); 27% (35)	↑AUC 8% (36)	No data	. . .	No data	No data
Delavirdine	↑AUC 2-fold (31, 32)†	No effect (31, 32)	↑AUC of HGC‡ 5-fold (31, 32)	↑AUC 113% ↓metabolite, AUC 50% (37, 40) Dose not established	No data	No data	. . .	No data
Efavirenz	↓AUC 30%†	↑AUC 18%	↓AUC 60%	↑AUC 20% ↓metabolite, AUC 37% (38, 39) No dose change	↓AUC 36% No dose change (29)	No data	No data	. . .

*Drugs in the vertical column are interacting drugs; those listed horizontally are the drugs affected by the interaction. Ellipses indicate data not applicable; arrows, the direction of the change of area under the curve (AUC): ↓, decrease; ↑, increase; and the numbers in parentheses, the reference citations. The possible dose changes are as follows: Indinavir, 400 mg twice daily, with ritonavir, 400 mg twice daily, based on pharmacokinetic study only. Nelfinavir, 750 mg 3 times daily, with saquinavir soft gel, 800 mg 3 times daily[41,78,79] or nelfinavir, 1250 mg twice daily, with saquinavir soft gel, 1000 mg twice daily.[42] Nelfinavir, 750 or 1000 mg, with indinavir, 1000 mg twice daily.[27,75] Ritonavir, 400 mg twice daily, with saquinavir soft-gel capsule (SGC) or hard-gel capsule (HGC), 400 mg twice daily.[26] Ritonavir, 400 mg twice daily with nelfinavir, 750 mg twice daily.[78] Delavirdine, 400 mg 3 times daily with indinavir, 400 mg or 600 mg 3 times daily.[31,32] Efavirenz, 600 mg daily, with indinavir, 1000 mg 3 times daily. Efavirenz, 600 mg daily, with saquinavir SGC, 400 mg twice daily, with ritonavir, 400 mg twice daily.

†A possible dose change may be necessary due to the interaction.

‡For these combinations, only data for the HGC formulation of saquinavir are available.

served, attributed to the contribution of longer-lived HIV-infected cell populations.[6] Release of trapped virions from follicular dendritic cell networks within lymphoid tissue may also contribute. Identification of the second phase of HIV decline led to the hypothesis that cellular HIV reservoirs might die off naturally (estimated half-life, 14-28 days) and that HIV might be eradicated after about 3 years of complete virus suppression.[6] Recent data have caused a modification of this concept.[7-10] There is a small but critical pool of resting memory $CD4^+$ lymphocytes that may contribute to persistence of replication-competent HIV in persons with viral suppression due to potent combination regimens for up to 2 years. Longevity of the cells is not known but may range from months to years, and the clinical relevance and biological significance (given the unphysiologic conditions of the studies) are uncertain. The practical implication is that in 1998 initiation of antiretroviral therapy represents a long-term commitment not to be undertaken lightly. Adherence, short-term and long-term adverse effects, impact on quality of life, and evolution of resistance must be addressed with each person considering treatment.

These studies, in addition to sounding a cautionary note, provide a positive message supporting use of potent combination antiretroviral regimens: despite isolation of infectious HIV from persons who had been virologically suppressed for more than 2 years, resistance mutations were not observed.[7-9] Also, prevention of emergence of resistance by viral suppression to below the 20- to 50-copies/mL threshold correlates with durability of virologic response to potent regimens.[11-13]

Use of potent therapy has resulted in remarkable declines in hospitalization rates, morbidity, and mortality where the drugs are available.[14-19] Furthermore, protease inhibitor (PI)–containing regimens can be cost-effective.[20,21]

Cautionary notes accompany these advances as follows: (1) virologic response rates to initial therapy with a PI and 2 nucleoside reverse transcriptase inhibitors (nRTIs) range from 60% to 90% and success of initial therapy is less likely as the disease advances; (2) durability of viral suppression beyond 2 years is uncertain; (3) close drug adherence is essential in preventing viral resistance, and current regimens are difficult[22,23]; (4) drug interactions resulting from hepatic metabolism of PIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs) increase therapeutic complexity (Table 1); (5) impact of extended treatment on quality of life is a major consideration; and (6) new and long-term adverse effects are appearing, particularly with PI-containing regimens.

Physicians and patients are faced with translating therapeutic principles embodied in the rapidly expanding knowledge base, in part not yet in peer-reviewed literature, into a practical approach to patient management. There are 11 approved antiretroviral drugs, including 5 nRTIs (zidovudine, didanosine, zalcitabine, lamivudine, and stavudine), 2 NNRTIs (nevirapine and delavirdine), and 4 potent PIs (ritonavir, indinavir, nelfinavir, and saquinavir [soft-gel capsule]). Four investigational drugs (abacavir, efavirenz, amprenavir, and adefovir dipovoxil) are in advanced stages of clinical evaluation (see http://www.ama-assn.org/special/hiv/library/library.htm). Choices for combination regimens are not a simple reflection of possible permutations derived from a list of available drugs. Practical issues such as drug compatibilities, adverse effects, and cross-resistance constrain the options available, especially when there is drug failure and resistance. Long-term strategies are essential to maximize therapeutic benefit over time—balancing potency, tolerance, regimen complexity, adverse effects, risk of resistance, and cost. These recommendations are designed to assist in moving toward this goal.

Table 2.—Examples of Alternative Regimens in Treatment Failure*

Initial Regimen	Alternative Following Treatment Failure
$nRTI_1/nRTI_2/PI_1$	$nRTI_3/nRTI_4/PI_2$
	$nRTI_3/nRTI_4/PI_2$/NNRTI
	PI_2/PI_3 with or without $nRTI_3/nRTI_4$ with or without NNRTI
$nRTI_1/nRTI_2$/NNRTI	$nRTI_3/nRTI_4/PI_1$
	PI_1/PI_2 with or without $nRTI_3/nRTI_4$
PI_1/PI_2 (with or without $nRTI_1/nRTI_2$)	$nRTI_1/nRTI_2$ (or $nRTI_3/nRTI_4$)/PI_3/NNRTI
	$nRTI_1/nRTI_2$ (or $nRTI_3/nRTI_4$)/PI_3/PI_4/NNRTI
$nRTI_1$ (with or without $nRTI_2$)/NNRTI/PI_1	$nRTI_2/nRTI_3$ (or $nRTI_3/nRTI_4$)/PI_2/PI_3
$nRTI_1/nRTI_2/nRTI_3$	$PI_1/PI_2/nRTI_4$
	PI_1/PI_2/NNRTI
	$PI_1/PI_2/nRTI_4$/NNRTI

*nRTI indicates nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; and NNRTI, nonnucleoside reverse transcriptase inhibitor.

INITIATING ANTIRETROVIRAL THERAPY

When to Initiate Therapy

There is no decisive new information regarding the optimal time to begin treatment. The point at which theoretical benefits of preventing immunologic damage are offset by realities of nonadherence or adverse effects is unknown. There is, however, growing consensus, as represented by recommendations of a Department of Health and Human Services (DHHS)–appointed panel, that early treatment initiation is associated with virologic, immunologic, and clinical benefits.[43] The International AIDS Society–USA panel continues to recommend antiretroviral therapy for any patient with established HIV infection and a confirmed plasma HIV-1 RNA level greater than 5000 to 10 000 copies/mL who is committed to the complex, long-term therapy. Accumulating data show that viral load is a strong, independent predictor of clinical outcome.[44,45] Degree and durability of virologic response correlate directly with plasma HIV RNA level and $CD4^+$ cell count at baseline. Treatment options should be discussed with all patients with HIV infection.

Pretreatment plasma HIV RNA level and $CD4^+$ cell count are important for evaluation of response to treatment. In general, prior to therapy initiation, 2 plasma viral load levels using the same technology and 2 $CD4^+$ cell counts should be obtained at 2 separate visits, at which times drug therapy options, implications, and requirements are discussed and reviewed. A baseline plasma HIV RNA level obtained using the more sensitive assays is not generally needed as more routinely available standard assays will suffice.

The first therapeutic intervention is the most important in achieving a maximum and durable virologic response as emergence of resistance may severely limit future treatment options. Although there are many reasons for drug failure, resistance secondary to poor adherence and suboptimal regimens may have the most serious long-term consequences. Therapy should not be initiated until treatment goals and need for close adherence to a regimen are understood and endorsed by the patient. Factors leading to reduced adherence may include drug adverse effects, inconvenient dosing schedules, high pill burden, interference with normal lifestyle, including food restrictions and hydration requirements, and competition from activities of daily living (eg, full-time employment or alcohol use).[46]

For asymptomatic patients with low plasma HIV RNA level (eg, <5000-10 000 copies/mL) and high $CD4^+$ cell count (eg, $>0.35\text{-}0.50 \times 10^9$/L [350-500/μL]) deferral of therapy with close follow-up may be appropriate given treatment complexities, risk of adverse effects, consequences of resistance, and the possibility that such persons may fall into the category broadly described as long-term nonprogressor. For those with low HIV RNA level (eg, <5000-10 000 copies/mL) and low $CD4^+$ cell count (eg, $<0.50 \times 10^9$/L and particularly $<0.35 \times 10^9$/L), therapy initiation is recommended, given independent prognostic significance of $CD4^+$ cell count and clinical trial data support.[44,47,48]

Initial Antiretroviral Regimens

The goal of antiretroviral therapy is to improve survival and decrease morbidity via continuous maximum suppression of HIV replication. Choice of a regimen should also take into consideration preservation of future treatment options should the initial regimen fail. Use of regimens that will durably reduce plasma HIV RNA below levels of detection of the most sensitive assays available is recommended with the expectation that such suppression will limit or prevent the development of resistance and provide durable clinical benefit. Although even modest reductions in viral load (eg, 0.5 to 1 log reductions) provide clinical benefit,[45,49-52] an approach that does not maximally suppress viral replication may lead to resistance and treatment failure, limiting treatment options.

Numerous clinical trials have been and are being conducted with combination antiretroviral regimens in treatment-naive patients. Most are designed with primary virologic not clinical end points, and many potentially effective combinations have not been directly compared or evaluated long term. However, an increasing number of drug combinations appear to have similar short-term potency. Thus, potential choices for a potent initial regimen are expanding. Examples of combinations in current use or under investigation for initial therapy include the following: (1) 1 PI and 2 nRTIs[19,53-67]; (2) 1 NNRTI and 2 nRTIs[68-73]; (3) 2 PIs with or without 1 or 2 nRTIs[74-80]; (4) 1 PI and 1 NNRTI with or without 1 or 2 nRTIs[36,69,81,83]; and (5) 3 nRTIs[83-85] (Table 2).

These regimens result in virologic success rates from 60% to 90% in antiretroviral-naive patients, as judged by achievement of a plasma HIV-1 RNA level less than 500 copies/mL at 24 weeks or beyond. The absence of data from randomized, comparative clinical trials makes it impossible to be certain of long-term superiority of one approach vs another. Considerations in this choice include strength of clinical trial data, potential for drug interactions with other necessary medications or exacerbation of underlying medical conditions (eg, neuropathy), likelihood of adherence, potential for long-term adverse effects, and preservation of future treatment options. Necessary commitment to years of therapy, cost and availability of drugs, and clinician familiarity with drugs and combinations are also important considerations in the choice of an initial regimen.

An increasing concern has been whether disease stage should dictate the approach. The panel cautions against any strictly "staged" approach to treatment; however, response rates decrease as HIV disease advances. For example, zidovudine-lamivudine-indinavir resulted in 45% to 85% of zidovudine-experienced subjects achieving viral loads below 500 copies/mL at 24 weeks, with lower response rates associated with low $CD4^+$ cell count and high viral load level at baseline.[53-55]

At this time, initiation of a potent PI and 2 nRTIs should remain the primary consideration, given the clinical trial data support for the durability of these combinations, and population-based data documenting reduced morbidity and mortality.[14-18,53,54,67] The place of dual PI–based combinations (typically combined with 2 nRTIs) as initial therapy is yet to be fully defined, but may be most appropriate for those with advanced

HIV disease. If deferral of a PI-containing regimen is desired, combination of an NNRTI with 2 nRTIs is an alternative approach. Regimens combining a PI with an NNRTI (with or without an nRTI) hold promise based on durable responses reported for the combination of indinavir and the experimental drug efavirenz through 60 weeks.[69,81] One concern with employing representatives of each of the 3 drug classes in an initial regimen is potential for multidrug-class resistance should the initial regimen fail. Data concerning initial potency of triple-nRTI–based regimens with the approved drugs (eg, zidovudine-didanosine-lamivudine)[83] or with zidovudine-lamivudine-abacavir are limited and durability of responses is uncertain.[85]

Constructing a potent combination from among the 3 current classes of drugs, nRTIs, NNRTIs, and PIs, requires thorough knowledge of their activities, adverse effects, and potential drug interactions.

Nucleoside Reverse Transcriptase Inhibitors

Although single nRTIs can be used as part of 3-drug and 4-drug combinations, dual nRTI combinations are most commonly used as components of such regimens. In antiretroviral-naive patients, there are several reasonable dual nRTI combinations for consideration as regimen components: zidovudine-lamivudine, stavudine-lamivudine, stavudine-didanosine, zidovudine-didanosine, didanosine-lamivudine, and zidovudine-zalcitabine. The first 3 combinations are the most commonly used. Lamivudine should be used only in regimens designed to be fully suppressive to prevent emergence of the lamivudine-associated M184V mutation and loss of its antiretroviral effect. The report[86] that zidovudine exposure can limit cell ability to phosphorylate stavudine on subsequent exposure needs confirmation; there are no data on ability of stavudine to affect subsequent zidovudine phosphorylation. Such data might influence the decision concerning which dual nRTI component to use initially. Combining zidovudine and stavudine should be avoided because of antagonism shown with this combination.

Nonnucleoside Reverse Transcriptase Inhibitors

Nevirapine was the first available compound in this class. Its activity in combination with zidovudine-didanosine in antiretroviral-naive patients led to the recommendation that an NNRTI–dual nRTI combination is a reasonable alternative to a PI–dual nRTI regimen in selected situations. Delavirdine has been shown to result in reasonable virologic responses when given in combination with zidovudine-lamivudine.[71] The investigational NNRTI efavirenz holds promise because of potency and potential for once-daily dosing (see http://www.ama-assn.org/special/hiv/library/library.htm). Potential for high-level resistance as a result of a single reverse transcriptase mutation suggests that drugs in this class should be used only in regimens designed to be maximally suppressive. Also, drug-drug interactions must be considered when NNRTIs are given with PIs (Table 1).

Protease Inhibitors

The major requirement for choice of PI is in vivo potency. Indinavir, ritonavir, and nelfinavir were each previously recommended as combination regimen elements. The new soft-gel capsule formulation of saquinavir (saquinavir-SGC) has enhanced bioavailability and, when given at recommended dosage in combination with zidovudine-lamivudine, produced virologic response comparable to that of indinavir-zidovudine-lamivudine through 24 weeks.[57] Saquinavir-SGC can thus be an additional consideration as a potent PI component, although experience with it is still limited. With respect to dual PI–based regimens, most data exist for ritonavir-saquinavir; durable virologic suppression has been reported through 60 weeks.[75] However, except with indinavir-saquinavir, in which in vitro antagonism has been shown, most dual PI combinations involving indinavir, ritonavir, nelfinavir, saquinavir, and the investigational drug amprenavir have been or will be investigated. Data are too preliminary for specific recommendations concerning these other dual PI combinations as initial therapy.

Strategies to enhance adherence are being addressed in several ways, eg, combining drugs in a single formulation (zidovudine-lamivudine). More convenient drug schedules are being explored, eg, studies of indinavir or nelfinavir, each administered in a twice-daily regimen in combination with zidovudine-lamivudine, report activity comparable to that of standard three-times-daily regimens through 32 and 24 weeks, respectively.[87,88]

CHANGING ANTIRETROVIRAL THERAPY

Considerations for Changing or Modifying Therapy

The basic indications for changing therapy, treatment failure, drug adverse effects, intolerance, and nonadherence, have not changed.[2] However, there are refinements in monitoring tools, increased complexity of the treatment failure definition, new considerations of treatment modification in absence of an adverse effect or drug failure, and increased recognition of the potential for long-term adverse effects.

Monitoring Response to Therapy

A major advance in monitoring has been development of plasma HIV RNA assays of increased sensitivity, which have a dynamic range of about 20 to 50 to about 50 000 copies/mL of plasma and are suitable for monitoring for the majority of patients on treatment. Assay precision at lower limits is yet to be defined, but assay results are generally reproducible when viewed as a detection tool at the 50-copies/mL lower limit. Assays will likely improve even further regarding lower limits of sensitivity. Small but careful studies involving potent regimens provide evidence for ongoing replication in patients with viral load consistently between 50 and 500 copies/mL.[7-9,89] In those with levels less than 50 copies/mL, evolution of resistance is restricted, although low levels of viral replication may persist. In other studies, durability of virologic response at 18 to 24 months was much greater when viral load was below a 20-copies/mL limit of assay detection than when it was in the 20 to 500 copies/mL range.[13,68]

The most sensitive assays available are thus recommended for continued monitoring of response to therapy. Frequency of viral load monitoring may need to be increased (eg, every 2 months) when using more sensitive assays to detect early viral rebound when re-establishment of control of viral replication is more likely possible. However, no definitive data exist to guide optimal monitoring frequency. Assay variation at low levels (eg, 50-200 copies/mL) will result in some patients having intermittently detectable virus. After treatment initiation, it may take longer (eg, >24 weeks) to reach a 50-copies/mL cutoff than it would a 500-copies/mL cutoff.

Other monitoring tools are entering the clinical arena or being developed. Although technologies to report codon alterations and phenotypic susceptibilities are being commercialized, there are unanswered questions concerning the role of resistance testing in routine clinical practice. The complex issues surrounding possible clinical application of resistance testing are described elsewhere.[90] $CD4^+$ cell subset determinations to enumerate memory and naive cells are being studied in clinical trials and may have a role in better defining degree of immune reconstitution. Therapeutic drug level monitoring is becoming available to clinicians, but its utility as a monitoring tool is a subject of considerable debate and cannot be recommended at this time.

Definition of Treatment Failure

The predicted use of plasma HIV RNA assays of increased sensitivity has focused more attention on defining treatment failure and its management. Treatment failure is a biologic continuum and has many variations. The strictest definition is that of confirmed detectable plasma HIV RNA (ie, >50 copies/mL) in an adherent patient who had achieved a viral load level below the detection limit and has not experienced a recent acute infectious illness or vaccination. Many such patients, however, are asymptomatic, have maintained good $CD4^+$ cell responses, and may have a favorable clinical prognosis (at least short term). The question arises as to whether treatment failure by this definition should mandate change in therapy. Continuing a regimen with low but detectable plasma viremia will be associated with viral evolution and gradual emergence of resistance, but this must be balanced against concern that premature treatment changes will constrain future options. There are no available prospective, comparative clinical trial data to assist clinicians with the issue of whether to change treatment at, for example, 50, 500, or 5000 copies/mL, and, thus, the decision should be individualized via discussion between patient and physician. However, evolution of resistance mutations continues when HIV is not maximally suppressed, and the greater possibility of success when treatment changes are made at lower HIV RNA levels suggest that an increasingly rigorous approach is warranted. This may be of most practical value for those experiencing their first confirmed drug failure. For those with their second or third regimen failure, the fewer options dictate a more conservative stance, with deferral of treatment changes until evidence of further increases in HIV RNA level or decreases in $CD4^+$ cell count. In these cases, patients should generally remain on the antecedent regimen until they can begin a new regimen. Accumulating data show that many patients continue to have immunologic and clinical benefit from potent regimens even after rebound viremia; for them, stopping therapy may result in further viral load increase, rendering re-establishment of adequate viral suppression more difficult.[91]

Other considerations regarding treatment failure are as follows: (1) the lack of initial virologic response that may result from poor adherence, inadequate drug absorption, or primary viral resistance; and (2) a falling $CD4^+$ cell count. When $CD4^+$ cell count decline occurs in concert with a rising HIV RNA level in an adherent patient, there is no question that treatment failure has occurred. The more difficult issue is a discordant response (eg, $CD4^+$ cell count decreases and HIV RNA level remains below the detection limit). The pathogenetic causes for this are uncertain, although drug adverse effect must be considered. For those with a confirmed CD4 cell decrease to below 0.10×10^9/L, or a confirmed rapid decrease, treatment changes may be useful. Although clinical disease progression remains an indication for treatment change, occurrence of an opportunistic infection must be considered in relation to the time of treatment initiation and virologic and immunologic status of the patient. New or recurrent opportunistic infections occurring during immune reconstitution and after potent therapy do not automatically mean treatment failure if occurring with a rising $CD4^+$ cell count or a low viral load or both.[92,93]

Modifications of Therapy in Absence of Treatment Failure or Adverse Effect

There has been increasing interest in considering treatment alterations not dictated by overt treatment failure or adverse effects, such as maintaining virus suppression with induction-maintenance regimens or enhancing regimens that appear effective without achieving maximal virus suppression (intensification). In composite data from 2 trials of induction-maintenance strategies, 3 to 6 months of induction with indinavir-zidovudine-lamivudine followed by randomization to zidovudine-lamivudine, zidovudine-indinavir, or indinavir monotherapy when the plasma HIV RNA level was below 200 to 500 copies/mL was inferior to continuing the 3-drug regimen.[22,23] These results, together with the observation that replication-competent virus was recovered from latent $CD4^+$ cell reservoirs for up to 2 years following potent therapy initiation,[7,9,91] suggest that longer duration of induction regimens, more potent maintenance regimens, or both may be needed.

For regimens achieving substantial early HIV RNA declines, but not below the limits of the most sensitive assay available, close monitoring in the first few months of treatment may permit addition of drug(s) to intensify the regimen and maximize long-term treatment benefit. The rationale for intensification is based on data suggesting that the HIV RNA nadir following initiation of an antiretroviral regimen is predictive of subsequent virus suppression and response durability.[11] However, the new drugs must be added before viral rebound occurs; otherwise, addition of a single new drug can be viewed as incremental therapy, which may promote resistance. There are no prospective, randomized, controlled clinical trials comparing intensification of an existing regimen with changing a regimen entirely if optimal early response is not achieved, but this is under study.

Although dual nRTI therapy alone is generally considered suboptimal, clinicians may face the dilemma of how to manage patients on dual nRTI regimens alone with HIV RNA levels below 500 copies/mL. In this situation, more sensitive assays may provide important information. If the HIV RNA concentration is in the 50 to 500 copies/mL range, treatment changes should be considered, and the principles outlined for selecting a new regimen in the setting of virologic failure should be employed. If the level is below 50 copies/mL, regimen continuation and close monitoring are reasonable.

Implications of Long-term Adverse Effects

There is increasing recognition of, and concern for, complications of long-term exposure to antiretroviral therapies, including hyperglycemia, hyperlipidemia, peripheral fat redistribution (lipodystrophy), and visceral fat accumulation.[94-97] Precise incidence, underlying pathogenetic mechanisms, and long-term implications of these derangements need defining. In general, their occurrence does not mandate change in therapy when a good therapeutic response is achieved. Their potential occurrence needs to be discussed with each patient prior to treatment initiation.

What to Change to

When the decision is made to change therapy, the approach should be driven by the underlying reason for the change. For adverse effects, intolerance, or suboptimal adherence to an otherwise successful regimen (ie, HIV RNA level below detection limits), selective substitution of individual, identifiable offending components is reasonable.

When a change in therapy is indicated due to drug failure, the same principles and considerations apply as described previously.[2] Efforts should be made to change the regimen in its entirety, using drugs with least potential for cross-resistance to current drugs. Cross-resistance among drugs within a class may be due to overlapping genotypic alterations conferred by individual drugs, unique pathways of multidrug resistance, intracellular pharmacologic interference (eg, zidovudine's potentially negative effect on stavudine phosphorylation), or less well-understood mechanisms, whereby one drug within a class may blunt subsequent response to other drugs in the

class.[98] The role of resistance testing in choosing alternative drugs is not fully defined. Absence of genotypic or phenotypic resistance in a given sample may simply mean that the responsible minor virus subpopulation is present at a frequency below detection limits of the assay.[90]

Given the increasing number of potential drug combinations, it is not possible to outline herein alternative regimens for every possible initial regimen. Table 2 illustrates general principles to be used in such decision making.

A most pressing clinical question in 1998 is how to manage patients in whom PI-containing regimens have failed. Prospective, randomized clinical trials to address this are ongoing or planned. Available data suggest that successful virologic suppression following failure on an initial regimen is more likely if a treatment alteration is made at a lower vs higher HIV RNA level.[99] However, data are lacking regarding durability of responses beyond 48 weeks. Use of dual PI–based regimens in combination with new nRTI(s) and an NNRTI (if not previously used) is the preferred approach currently, but more data to support this are necessary. The role of investigational drugs as components of alternative regimens is being defined via ongoing clinical trials; however, cross-resistance to currently approved drugs may prove limiting in many instances. Other approaches may include adjunctive modalities such as hydroxyurea.[100] Hydroxyurea enhances didanosine by altering normal nucleotide pool size,[101] but its efficacy and safety in this setting are not established.

When to Stop Therapy

Eradication of HIV with maximally suppressive therapy alone for 2 years is unlikely given the present understanding of HIV pathogenesis; thus, therapy should be continued as long as possible. Even with virologic failure, many patients maintain clinical and immunologic benefit.[91] After attempts to adjust the drug regimen to suppress replication are made, therapy should be continued in the face of virologic failure, if evidence of clinical and immunologic stability exists. In general, stopping all antiretroviral therapy is reasonable when the patient, after discussion with the physician, believes that the adverse effects outweigh potential benefits of therapy.

SPECIAL CONSIDERATIONS

Primary Infection

Immediate initiation of potent therapy appears warranted when primary HIV infection is identified. Recent data indicating immunologic benefit of such therapy when initiated before seroconversion support antiretroviral intervention in primary infection.[102] Selection of the regimen must balance potential benefits with the possible difficulties in adherence. While viral eradication in established HIV infection may not be possible with available antiretroviral drugs, the possibility of eradication in early primary infection remains. Patients with primary HIV infection should be referred to clinical trials if possible so these strategies can be systematically investigated. Strategies that seek to limit cellular activation and cellular targets for HIV infection are being investigated.[103]

HIV Infection in Pregnancy

This topic has been reviewed extensively by a US Public Health Service task force.[104] In most respects, HIV infection in pregnant women should be treated as in infection in nonpregnant patients. There are situations, however, in which therapy may be altered in the pregnancy setting. If HIV infection and pregnancy are simultaneously identified during the first trimester or if the pregnant woman has early-stage HIV disease, it may be preferable to defer therapy to the second trimester, at which time potent combination treatment can be initiated. For asymptomatic pregnant women with low HIV RNA levels and high $CD4^+$ cell counts, the 2 goals of antiretroviral therapy are to prevent perinatal transmission and avoid compromising subsequent response to therapy for the women. Although the US Public Health Service guidelines recommend zidovudine alone as a possible option,[104] many physicians prescribe potent combination therapy to minimize the possibility that resistance will develop in the mother as a result of suboptimal therapy during pregnancy. However, given available data, zidovudine should probably be included in any regimen intended to prevent perinatal transmission.

Clinical trials are exploring new strategies for the timing of therapy for mother and child and for specific therapeutic options for maximally effective transmission prevention. Since experience in several regions indicated that antiretroviral therapy[105,106] can reduce risk of perinatal transmission to about 4%, there is hope that more effective interventions will prevent it entirely. Women taking antiretrovirals during pregnancy should be encouraged to enroll in the Antiretroviral Pregnancy Registry (telephone number: [800] 722-9292, ext 38465).

Table 3.—Clinical Management Issues Regarding Antiretroviral Therapy for Which Existing Data Are Incomplete

- When precisely should therapy be started? At what point is the theoretical benefit of preventing immunologic damage offset by the realities of nonadherence or adverse effects?
- What is the optimal initial antiretroviral regimen? Is a protease inhibitor–containing regimen always preferable? Is a nonnucleoside reverse transcriptase inhibitor an adequate substitution for a protease inhibitor in a 3-drug regimen?
- Should the complexity and potency of the starting regimen be adjusted according to the patient's disease stage?
- Are regimens that use potent combinations directed at a single viral enzyme better in the long term than multiple target regimens when the difficulty of secondary treatment is considered?
- Given that most patients achieve plasma human immunodeficiency virus RNA levels below detection limits with assays with lower limits of detection of 500 copies/mL and of 20 to 50 copies/mL, does the more sensitive test add value to management that offsets potential confusion or the too rapid abandonment of a given regimen?
- Given the durability of immunologic response even with relative virologic failure, when is the optimal time to abandon a drug or drugs when plasma virus load becomes detectable?

Postexposure Prophylaxis

Risk of HIV infection associated with unintended sexual or needle exposure to HIV is probably comparable to occupational risk in medical personnel who have accidental puncture wounds. Benefits of postexposure prophylaxis have been established in occupational settings, and immediate initiation of potent combination antiretroviral therapy consisting of 2 or more drugs is recommended for high-risk occupational exposures. If exposure to resistant virus is suspected, a maximally suppressive regimen of drugs to which the virus is likely susceptible should be chosen. According to the Centers for Disease Control and Prevention guidelines, therapy should continue for 4 weeks.[107] Laboratory evaluations for antiretroviral adverse effects after 2 weeks should be considered. Health care workers who receive chemoprophylaxis for HIV exposure should be encouraged to enroll in the Centers for Disease Control and Prevention registry (telephone number: [888] HIV-4PEP, ie, [888] 737-4448).

Concerns have been raised regarding routine provision of postexposure prophylaxis for sexual and needle-sharing HIV exposures,[108] eg, the risk of exposing many people to therapy and associated adverse effects, especially when index case HIV status is unknown and there is the possibility that treatment availability might result in an increase in less safe behaviors. Other issues include the likelihood that sexual and needle-sharing exposures are often repeated and would require repeated treatment courses, and cost implications of provid-

ing widespread postexposure treatment to persons with low risk of infection when financial constraints already exist for providing therapy to persons known to be infected. Because the risk-benefit ratio for prophylaxis in these settings is not known, it is premature to make general recommendations at this time. Pilot investigations are under way to explore these issues. Meanwhile, if the decision is made to initiate prophylaxis, the principles regarding use of potent combination therapy for occupational exposures should be followed. Any such initiation of prophylaxis should be coupled with education designed to decrease the probability of repeated exposure. Recommendations for postexposure prophylaxis should be made by or in consultation with physicians experienced in antiretroviral drug management.

SUMMARY

The above recommendations are intended to provide a summary of current information about management of HIV infection with potent antiretroviral regimens. There are clinical settings for which definitive data are not yet available (Table 3). The panel will continue to monitor research findings in the field and provide updated recommendations as necessary.

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