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Consensus Statement

Antiretroviral Therapy for HIV Infection in 1997

Updated Recommendations of the International AIDS Society–USA Panel

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Objective.—To provide current recommendations for antiretroviral therapy for human immunodeficiency virus (HIV) disease.

Participants.—The original International AIDS Society–USA 13-member panel representing international expertise in antiretroviral research and care of patients with HIV infection.

Evidence.—The following were considered: Newly available clinical and basic science study results, including phase 3 controlled trials; clinical, virological, and immunologic end-point data; interim analyses of studies presented at national and international research conferences; studies of HIV pathophysiology; and expert opinions of panel members. Recommendations were limited to the drugs available in mid 1997.

Process.—The full panel met on a regular basis (July 1996, September 1996, November 1996, January 1997, and April 1997) since the publication of its initial recommendations in mid 1996 to review new research reports and interim results. The panel discussed whether and how new information changed its initial recommendations. The recommendations contained herein were determined by group consensus.

Conclusions.—New data have provided a stronger rationale for earlier initiation of more aggressive therapy than previously recommended and reinforce the importance of careful selection of initial drug regimen for each patient for optimal long-term clinical benefit and adherence. The plasma viral load is a crucial element of clinical management for assessing prognosis and the effectiveness of therapy, and such testing must be done properly. Treatment failure is most readily indicated by a rising plasma HIV RNA level and should be confirmed prior to a change of treatment. Therapeutic approaches must be updated as new data, particularly on the long-term clinical effect of aggressive antiretroviral treatment, continue to emerge.

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NEW INFORMATION on human immunodeficiency virus (HIV) pathogenesis, viral load monitoring, and the impact of potent antiretroviral drug regimens has emerged since the publication of the International AIDS Society–USA recommendations for antiretroviral therapy in July 1996.[1] These developments have led the panel to review and update its recommendations. As stated in the original report, the process is one of continuous reevaluation in order to provide clinicians with recommendations that reflect an ongoing synthesis of the latest developments in basic science, drug development, and clinical investigation. These updated recommendations are an extension of the previous guidelines and apply the same principle of translating the increased understanding of HIV disease pathogenesis into therapeutic approaches.

SCIENTIFIC RATIONALE FOR UPDATED RECOMMENDATIONS

The key element in HIV pathogenesis is the high level of productive infection, which is characterized by a high rate of virion turnover.[2-6] Current estimates suggest that at least 10 billion HIV particles are produced and destroyed each day and that the plasma virus half-life is about 6 hours; $CD4^+$ cell turnover rates may be similar.[4,5] Studies of HIV DNA and RNA in lymphoid tissue provide direct evidence of high-level replication that is paralleled by detection of virus particles in plasma,[7,8] and even moderate levels of plasma HIV RNA are associated with active HIV replication in lymphoreticular tissue. These changes reflect intense viral activity within lymphoreticular tissues that ultimately destroys key parts of the lymphoid system.[2,9] The level of HIV RNA expression in lymphoid tissue may be higher and more intense than the plasma concentration would suggest.[9] Thus, even moderate levels of plasma HIV RNA appear to reflect very active HIV replication in those tissues.

Data continue to emerge with respect to HIV in important body compartments beyond the blood and lymphoid tissue. Viral load levels in genital secretions and cerebrospinal fluid are not simple reflections of plasma concentration.[10,11] Local HIV replication within these compartments can be influenced by local processes, such as concomitant sexually transmitted diseases in the case of the genital tract. Decreases in plasma HIV RNA concentration induced by antiretroviral therapy are usually but not always accompanied by decreases in the genital tract.[12,13] Therefore, reductions of HIV RNA expression to below the limits of assay detection in genital secretions should not be interpreted to mean that an individual is noninfectious, and it is not clear what impact treatment-induced reductions in HIV RNA in genital secretions may have on risk of sexual transmission.

The laboratory tool that has contributed most to the increased understanding of viral pathogenesis and antiretroviral efficacy is quantitation of HIV RNA in plasma. In natural history studies and in controlled clinical trials, the level of HIV RNA in plasma has been shown to be the strongest predictor of outcome over 1- to 10-year periods of observation.[14-17] Although there is a continuum of risk over the range of measurable plasma HIV RNA levels, no lower limit threshold has been defined. For example, even patients with plasma HIV RNA levels below 5000 copies/mL have measurable, albeit low rates of clinical progression.[1,18] In addition, declines in plasma HIV RNA concentrations during therapy are strongly associated with a decrease in risk of subsequent disease progression.[19-21]

Despite the strength of plasma viral load quantitation as a prognostic marker and its usefulness in therapeutic monitoring, a number of caveats are important: (1) single determinations of HIV RNA levels need to be interpreted cautiously given the problems that can result from improper or inconsistent specimen handling and processing, assay variability, and the effect of recent vaccinations and intercurrent infections[22-25]; (2) variability among currently available assays may result in differences in plasma HIV RNA levels; levels determined by target amplification assays (eg, reverse transcriptase polymerase chain reaction [RT-PCR]) may give values that are as much as 2-fold higher than values given by signal amplification assays (eg, branched DNA [bDNA]); (3) although reductions of plasma HIV RNA in the setting of controlled clinical trials are associated with significant reductions in risk of disease progression, the degree of clinical benefit conferred by a specific treatment or class of antiretroviral drugs (ie, the surrogacy for clinical treatment effect) has not been completely defined[26]; (4) other independent predictors of clinical outcome, although less powerful than virus load, have been identified in multivariate analyses, including the biologic phenotype (syncytium-inducing capacity) of the virus and the CD4+ cell count[15,27,28]; and (5) new determinants of disease progression, such as genetic polymorphism at the *CCR5* locus, are being defined.[29,30] Plasma HIV RNA level does, however, provide essential information, and lack of access to HIV RNA testing greatly limits the effective clinical management of HIV-infected patients.

Against this background, effects of potent antiretroviral regimens are being increasingly well characterized. In this discussion, it is the potency of a therapeutic regimen that is important and not the number of drugs per se. Nevertheless, for practical purposes at this point, given the currently approved antiretroviral drugs, this translates into 3-drug regimens that usually include 2 nucleoside analog reverse transcriptase inhibitors (NRTIs) and a protease inhibitor with strong in vivo potency (eg, indinavir, ritonavir, nelfinavir). For example, the combination of zidovudine, lamivudine, and indinavir reduced plasma HIV RNA levels below 500 copies/mL in 85% of subjects and below 50 copies/mL in 75% of subjects for at least 68 weeks in zidovudine-experienced subjects with CD4+ cell counts between 0.050×10^9/L (50/µL) and 0.40×10^9/L (400/µL).[31,32] In another study, this regimen reduced plasma HIV RNA levels to below 500 copies/mL in 65% of patients for at least 24 weeks in zidovudine-experienced patients with CD4+ cell counts less than 0.050×10^9/L (50/µL).[33] This regimen is presumably even more potent in zidovudine-naive subjects, and similar results have been seen with other 3-drug regimens such as zidovudine and lamivudine combined with ritonavir or nelfinavir.[34,35] Both the degree and durability of viral suppression in the plasma and the lymphoid tissue is greater with protease inhibitor–containing regimens than that seen with double-NRTI regimens. Three-drug regimens such as these have shown, in a limited number of subjects, that viral resistance can be delayed by potent virus suppression. The clinical benefit conferred by indinavir in combination with zidovudine or stavudine plus lamivudine has recently been shown in a large controlled trial of zidovudine-experienced patients with CD4+ counts below 0.20×10^9/L (200/µL).[36] Reductions in mortality and clinical progression rates have been previously reported with regimens containing ritonavir or saquinavir.[37,38]

Despite the impressive immunologic, virological, and clinical responses seen with protease inhibitor–containing regimens when such therapy is initiated in moderately advanced disease, the restoration of CD4+ cells typically is incomplete with respect to number, proportions of naive vs memory cells, and breadth of the T-cell receptor repertoire.[39,40] Since the ultimate goal of antiretroviral therapy is to prevent immunologic and clinical sequelae, the incomplete immune restoration seen thus far argues in favor of earlier intervention to prevent irreversible immune deficits.

The rapid viral proliferation and the extraordinary turnover rate have major implications for antiretroviral therapy with respect to the aggressiveness and timing of intervention. Given the inherent error rate of the HIV reverse transcriptase, it has been estimated that every possible base pair of the HIV genome probably mutates on a daily basis.[6,41] Thus, it is not surprising that monotherapy or combination regimens that only partially suppress viral replication allow more rapid selection of resistant variants and ultimately contribute to therapeutic failure. Taken together, the above data provide a scientific rationale for a more aggressive therapeutic stance. These new recommendations must be tempered by the fact that reduction of the plasma viral load to below the levels of detection of current assays does not necessarily indicate the complete suppression of viral replication. Further, durability of effect beyond 2 years and long-term tolerance of 3-drug regimens have not yet been demonstrated. However, current data provide strong support for updating the 1996 recommendations of the panel.

INITIATING ANTIRETROVIRAL THERAPY

When to Initiate Therapy

The panel previously recommended therapy for HIV-infected individuals with symptomatic HIV disease, those with CD4+ cell counts less than 0.50×10^9/L (500/µL)—particularly below 0.35×10^9/L (350/µL)—and those with plasma HIV RNA concentrations above the range of about 30 000 to 50 000 copies/mL[1]; therapy was to be considered for individuals with plasma HIV RNA levels greater than

Table 1. Considerations for Initiating Antiretroviral Therapy

Therapy is recommended for all patients with human immunodeficiency virus (HIV) RNA levels above 5000 to 10 000 copies/mL of plasma
Therapy should be considered for all HIV-infected patients with detectable HIV RNA in plasma (see text)
For patients at low risk of progression (low plasma HIV RNA level and high CD4+ count), particularly those who are not committed to complex antiretroviral regimens, therapy might be safely deferred. These patients should be reevaluated every 3 to 6 months (see text)

Table 2.—Selected Options for Initial Therapy*†

Regimen‡§	Advantages	Disadvantages
NRTI-1, and NRTI-2, and PI	This regimen should be able to achieve plasma HIV RNA levels below limit of detection in large majority of drug-adherent patients	Strict adherence to this regimen is crucial; quality of life may be affected; durability of effect, long-term tolerance, and overall clinical benefit in antiretroviral-naive patients with early disease is not fully defined
NRTI-1, and NRTI-2, and NNRTI	Many patients taking this regimen achieve plasma HIV RNA levels below limit of detection; it also permits deferral of a PI if this option is chosen	Strict adherence to this regimen is crucial; may not be as potent as a PI-containing regimen; it is not recommended for patients with advanced disease (ie, low CD4+ counts or high plasma viral load); durability of effect and overall clinical benefit not fully defined

*NRTI indicates nucleoside analog reverse transcriptase inhibitor; PI, protease inhibitor; HIV, human immunodeficiency virus; and NNRTI, nonnucleoside reverse transcriptase inhibitor. Numerals 1 and 2 indicate different entities in a class of drugs.

†Potent regimens, exemplified by currently available 3-drug combinations, are listed. Careful consultation with the patient to discuss the need for long-term commitment to a complex regimen is essential before initiating triple-drug therapy. Double-NRTI combinations have a role in defined circumstances (see text). Other combinations (eg, double–protease inhibitor regimens) are under study.

‡Acceptable combinations of 2 NRTIs include either zidovudine combined with lamivudine, didanosine, or zalcitabine, or stavudine combined with lamivudine or didanosine. Protease inhibitors with potent in vivo activity are recommended; currently these include indinavir, ritonavir, and nelfinavir.

§Of the currently approved NNRTIs, nevirapine and delavirdine, data are only available for the effectiveness of nevirapine for this application.

5000 to 10 000 copies/mL. Therapy is now recommended for all patients with plasma HIV RNA concentrations greater than 5000 to 10 000 copies/mL regardless of $CD4^+$ cell count (Table 1). Data do not permit an absolute plasma HIV RNA threshold for initiation of therapy. There is variability among different assays (eg, bDNA, RT-PCR, nucleic acid sequence-based amplification [NASBA]), variable levels of detection among different generations of the same assay, and different end points used in several clinical trials. As noted, plasma HIV RNA values obtained by different viral load assays may vary. Thus, HIV RNA levels should be obtained using the same assay (eg, RT-PCR, bDNA, or NASBA) for every sample from any one single patient. Recommending an absolute number rather than a range of values would suggest a level of certainty that has not been achieved.

Therapy should be considered for all subjects with HIV infection and detectable plasma HIV RNA who request it and are committed to lifelong adherence to the necessary treatment. For patients with low plasma HIV RNA levels and high $CD4^+$ cell counts, therapy might be safely deferred in the short term with reevaluation of plasma HIV RNA level every 3 to 6 months. A small minority of subjects who may be true long-term nonprogressors or slow progressors might be identified with this approach.

Therapy continues to be recommended for patients with symptomatic HIV disease or with $CD4^+$ cell counts below 0.50×10^9/L (500/µL), particularly below 0.35×10^9/L (350/µL). The latter recommendation is especially important in situations in which HIV RNA assays are not available.

Initial Antiretroviral Regimens

The previous recommendations, which centered on double-NRTI regimens, were based on data available at the time.[18,42,48] The inclusion of a protease inhibitor in initial regimens was considered reasonable for any patient and was recommended for patients at high risk of short-term progression. The panel now recommends that the preferred initial regimen is one that is most likely to reduce and maintain plasma HIV RNA levels below the level of detection (eg, currently below 500 or 400 copies/mL, depending on the assay) using the most sensitive assays available. Currently, such a regimen would include 2 NRTIs and a protease inhibitor with high in vivo potency (Table 2). Whether double-NRTI regimens would be as effective as more potent triple-drug regimens in suppressing viral replication in patients with low plasma viral load levels (eg, <10 000 copies/mL) is unknown.

Prior to initiating a triple-drug regimen, a detailed discussion between patient and physician is necessary to assess fully the patient's ability and willingness to commit to a complex, costly, and potentially toxic regimen. This is a particular concern in asymptomatic patients at an early disease stage, as ability to maintain long-term adherence to the regimen is a major challenge. Less than excellent adherence may result in virus breakthrough and emergence of drug-resistant strains. Even short-term nonadherence to an aggressive therapy may result in rapid virus repopulation in lymph nodes.[31,35,44] Given the potential for cross-resistance among the available protease inhibitors, the efficacy of future treatment options could be severely compromised by less than excellent adherence.[45] For example, use of indinavir may select for resistance mutations that decrease the likelihood of responding to subsequent therapy with ritonavir and vice versa. Cross-resistance among protease inhibitors may pose a major challenge for patients whose virus has broken through an initial protease inhibitor–containing combination. Although genotypic or phenotypic laboratory assays of drug resistance may, in the future, prove helpful in selecting alternative regimens, well-validated, reasonably priced, and rapid assays of resistance are not currently available for patient management.

Although a 3-drug regimen containing a protease inhibitor is the preferred initial regimen because of its potency, it may not be practical for every patient. The primary recommended alternative is a combination of 2 NRTIs plus a nonnucleoside reverse transcriptase inhibitor (NNRTI). In the INCAS trial, nevirapine in combination with zidovudine and didanosine in antiretroviral-naive subjects with $CD4^+$ cell counts of 0.20×10^9/L (200/µL) to 0.60×10^9/L (600/µL) reduced plasma HIV RNA concentrations to below 20 copies/mL in 55% of patients for at least 52 weeks.[46,47] There have been few direct comparisons of protease inhibitor– and NNRTI-containing 3-drug regimens (eg, zidovudine, lamivudine, and indinavir vs zidovudine, didanosine, and nevirapine), but extent and duration of suppression of plasma virus appear to be greater with a potent protease inhibitor–containing regimen. The INCAS trial has established an important principle in the use of currently available NNRTIs, in that their activity is maximized when combined with other drugs to which the patient is naive.[46,47] The INCAS trial results are consistent with the thesis that potent suppression can prevent the early emergence of resistance as, in a limited number of isolates studied thus far, nevirapine resistance has been prevented for at least 52 weeks in a clinical trial setting.[48]

Data on double protease inhibitor combinations (eg, ritonavir and saquinavir) and 3-drug regimens that combine an NRTI, an NNRTI, and a protease inhibitor are not yet sufficient to determine the role of these approaches for initial therapy. The combination of ritonavir and saquinavir,[49] for example, looks promising, with a high proportion of patients achieving plasma HIV RNA levels below level of detection at 20 weeks; similar preliminary data are emerging for other double protease inhibitor regimens. Pharmacokinetic interaction and marker efficacy data with regard to other double protease inhibitor regimens or protease inhibitor and NNRTI combinations are currently too fragmentary to recommend these as initial regimens.

For patients in whom initial regimens with protease inhibitors or NNRTIs are not appropriate or not possible (because of lack of commitment to drug adherence, access, cost, etc), alternatives exist but compromises are associated with each. For a patient at low risk of progression (eg, asymptomatic with high CD4+ cell count and low plasma HIV RNA concentration) who is not committed to use of a complex 3-drug regimen, it may be reasonable to defer therapy and to monitor CD4+ cell count and plasma HIV RNA concentration until the patient is prepared to initiate so demanding a regimen.

However, for patients who are not candidates for triple-drug regimens and are considered at high risk of short-term disease progression, deferral is not recommended; initiation of a double-NRTI regimen is preferred to no therapy for such patients. The combination of zidovudine and didanosine or of zidovudine and zalcitabine[18,42] has been shown to have greater clinical benefit than zidovudine monotherapy in antiretroviral-naive patients; zidovudine and lamivudine have also been shown to confer clinical benefit.[50,51] Two other regimens, stavudine and didanosine[52] and stavudine and lamivudine[53] have each demonstrated plasma HIV RNA reductions of approximately 1.5 log in antiretroviral-naive patients and offer the convenience of twice-daily dosing. Each of these 5 double-NRTI regimens may be used as stand-alone therapies in the circumstances described above, although they are more appropriately used as part of 3-drug combinations with a protease inhibitor or an NNRTI. As noted, an unresolved issue is whether a double-NRTI regimen might adequately suppress plasma HIV RNA in a subset of patients with relatively low viral load levels (eg, <10 000 copies/mL). If a 2-NRTI regimen is used in this setting, more frequent viral load monitoring is necessary so that a more aggressive treatment regimen can be initiated promptly if there is a significant sustained increase in plasma HIV RNA level. Within the context of the discussion of the degree of viral suppression achieved with 2-NRTI regimens, lamivudine-containing 2-NRTI regimens (eg, zidovudine and lamivudine or stavudine and lamivudine, without a protease inhibitor or an NNRTI) should be chosen only after very careful consideration. While lamivudine is generally well tolerated, the rapid development of lamivudine resistance in less completely suppressive antiretroviral regimens, mediated by the M184V substitution, may limit the potential usefulness of this drug in future regimens that contain protease inhibitors.[50,54]

At the present time, monotherapy with any of the available antiretroviral drugs is not recommended for initiation of treatment of HIV disease. Viral resistance mutations usually emerge within weeks to months with monotherapy. At best, monotherapy causes a transient decrease in plasma viral load but compromises future effective therapies by selecting for viral mutants that are resistant to 1 or more antiretroviral drugs.

CHANGING ANTIRETROVIRAL THERAPY

Considerations for Changing Therapy

The reasons for changing therapy remain as initially stated: treatment failure, toxic effects, intolerance, nonadherence, and current use of a suboptimal regimen (Table 3). While there are no data from controlled clinical trials that establish precise criteria for treatment failure, the definition of treatment failure has been refined to reflect the current availability of several potent regimens, the strong scientific rationale for strict control of viral replication, and the realization of the consequences of ongoing viral replication regarding rapid emergence of drug-resistant mutants and progressive immunologic compromise. Hypothetically, changing therapy while plasma HIV RNA levels are relatively low may limit the degree of viral resistance that may emerge and may increase the opportunity for successful resuppression with an alternative regimen.

As a general guideline for patients who have achieved plasma viral load levels below detectable limits (particularly those who are taking protease inhibitor–containing regimens), a change is recommended if the plasma HIV RNA concentration is confirmed to have increased. Ideally, any confirmed detectable plasma HIV RNA level is an indication to change therapy, in order to prevent drug-resistant viral mutants. From a practical standpoint, given the limited numbers of alternative antiretroviral drugs, it may be reasonable to await a documented increase in plasma HIV RNA level to greater than 2000 to 5000 copies/mL before changing therapy in this setting. For a patient who has had an initially significant decrease in HIV RNA level, but not to below detection limits, a confirmed increase to greater than 5000 to 10 000 copies/mL should indicate a treatment change. A careful assessment of adherence should always be made prior to changing therapy, preferably at the time the viral load is determined. Factors other than viral resistance can lead to loss of viral suppression: these include nonadherence, recent vaccinations, and intercurrent illnesses.

Table 3.—Indications for Changing Therapy

Treatment failure, as suggested by a confirmed rising plasma human immunodeficiency virus RNA level or failure to achieve the desired reduction in plasma viral load; declining CD4+ cell count; or clinical disease progression
Unacceptable toxicity of, intolerance of, or nonadherence to the regimen
Current use of suboptimal treatment regimens, ie, antiretroviral monotherapy

One must be especially careful not to prematurely abandon a given regimen shortly after the initiation of therapy. For example, a regimen with in vivo biological activity will significantly decrease plasma HIV RNA levels within 2 to 4 weeks of initiating therapy; in patients with high pretreatment plasma viral load levels, maximal suppression may not be seen until 12 to 24 weeks of potent therapy because of the slower "second phase" decline after the initial drop in plasma HIV RNA.[44]

A dilemma is presented for patients who achieve a substantial initial reduction in plasma HIV concentration, on the order of 1.5 to 2.0 log, but whose plasma viral load levels do not fall below the level of detection. Abandonment of the regimen is not necessarily indicated, and an alternative approach might be continued therapy with close observation until there is a confirmed substantial rise above the maximal reduction achieved.

Other indications of treatment failure remain as previously stated: lack of an initial virological response, return to pretreatment plasma HIV RNA levels, declining CD4+ cell count, or clinical disease progression. Complicating this definition somewhat is a phenomenon increasingly reported with protease inhibitor–containing regimens, ie, discordance between plasma HIV RNA level and CD4+ cell count that may occur several weeks or months into therapy. Discordance occurs when the plasma HIV RNA concentration returns to or near the pretreatment level while the CD4+ cell count remains substantially above the pretreatment

Table 4.—Examples of Alternative Antiretroviral Regimens for Treatment Failure on 3-Drug Regimens*†

Initial Regimen	Alternative Combinations
Zidovudine-lamivudine-protease inhibitor-1	Stavudine-didanosine-protease inhibitor-2‡ Stavudine-didanosine-NNRTI§ Ritonavir-saquinavir-NRTI‖
Stavudine-lamivudine-protease inhibitor-1	Zidovudine-didanosine-protease inhibitor-2‡ Zidovudine-didanosine-NNRTI§ Ritonavir-saquinavir-NRTI‖
Zidovudine-didanosine-protease inhibitor-1	Stavudine-lamivudine-protease inhibitor-2‡ Stavudine-lamivudine-NNRTI§ Ritonavir-saquinavir-NRTI‖
Stavudine-didanosine-protease inhibitor-1	Zidovudine-lamivudine-protease inhibitor-2‡ Zidovudine-lamivudine-NNRTI§ Ritonavir-saquinavir-NRTI‖
Zidovudine-didanosine-NNRTI	Stavudine-lamivudine-protease inhibitor-1 Zidovudine-lamivudine-protease inhibitor-1

*NRTI indicates nucleoside analog reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; and PI, protease inhibitor. Numerals 1 and 2 indicate different entities in a class of drugs.

†Regimens listed are examples of potential alternatives for initial regimens listed in Table 1 and are not meant to be all-inclusive. The principle of switching 2 or 3 new drugs is indicated when failure on the initial regimen has occurred. In practice, options are limited beyond the first alternative, and a component of a prior regimen may need to be continued or recycled after failure of a second or third regimen. The NRTI-NNRTI-PI regimens are under study, but pharmacokinetic interaction and safety data are not available.

‡The best alternative PI after failure on initial PI-containing regimen is unknown. Cross-resistance between indinavir and ritonavir is nearly complete. Thus, virological failure (as opposed to intolerance) of one may severely limit the use of the other. Indinavir or ritonavir may or may not select for cross-resistance to nelfinavir.

§The use of a currently available NNRTI is unlikely to result in suppression of plasma human immunodeficiency virus RNA below detection levels in antiretroviral-experienced patients.

‖Efficacy of ritonavir and saquinavir and 1 or more NRTI in combination in this circumstance is unclear and is under study. Other double-PI combinations are under study.

Table 5.—Examples of Alternative Antiretroviral Regimens for Treatment Failure on a Double-NRTI Combination*†

Initial Regimen	Alternative Combinations
Zidovudine-didanosine	Zidovudine-lamivudine-protease inhibitor‡ Stavudine-lamivudine-protease inhibitor‡§ Ritonavir-saquinavir-NRTI‖
Zidovudine-zalcitabine	Zidovudine-lamivudine-protease inhibitor‡ Stavudine-lamivudine-protease inhibitor‡§ Stavudine-didanosine-protease inhibitor‡§ Ritonavir-saquinavir-NRTI‖
Zidovudine-lamivudine	Stavudine-didanosine-protease inhibitor‡§ Ritonavir-saquinavir-NRTI§‖
Stavudine-didanosine	Zidovudine-lamivudine-protease inhibitor‡ Ritonavir-saquinavir-NRTI‖
Stavudine-lamivudine	Zidovudine-didanosine-protease inhibitor‡ Ritonavir-saquinavir-NRTI§‖

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

†Regimens listed are examples of potential alternative combinations and are not meant to be all-inclusive. The principle of switching 2 or 3 new drugs is indicated when failure on an initial, double NRTI regimen has occurred. Regimens containing an NNRTI plus a PI are under development and should be used only when full pharmacokinetic interaction and safety data are available.

‡Protease inhibitors with potent in vivo activity are recommended; currently these include indinavir, ritonavir, and nelfinavir.

§If the patient or physician wishes to defer PI use, an NNRTI could be substituted, but suppression of plasma human immunodeficiency virus RNA below the level of detectability with NNRTIs has not yet been documented in patients with prior antiretroviral experience.

‖Optimum strategic use of double-PI combinations (eg, ritonavir and saquinavir with 1 or more NRTI) is unclear. Whether it is preferable to employ them in this circumstance or after failure on a single PI has not been determined. Other double-PI combinations are under study.

level. Although the pathophysiological basis for this is not clear at present, the basic concept is that HIV replication is the driving force in disease progression, and changing therapy in this circumstance is recommended as long as alternative regimens exist. Conversely, discordance may also occur with a sustained decrease in viral load below detectable limits but a $CD4^+$ cell count that falls progressively. In this situation, there are no clinical data to guide practice, but many experts would recommend changing antiretroviral regimen if the $CD4^+$ cell count is falling rapidly or progressively.

When toxic effects emerge that do not permit treatment continuation, dose reductions of the protease inhibitor component should be avoided if at all possible. If the toxic effect is characteristic of one of the NRTIs (eg, pancreatitis related to didanosine), the presumed offending drug should be stopped; after the toxic effect has resolved, the offending drug should be replaced with an NRTI with a different toxicity profile. If the basis for the toxic effect is unclear, brief and complete interruption of the full therapeutic regimen is generally preferred. Following resolution of the toxic effect, clinical judgment (based in part on available alternative drugs that may be appropriate for the patient) is necessary to determine whether to replace 1 drug in the initial regimen or to change to an entirely new 3-drug regimen.

Patients currently taking regimens of 2 NRTIs alone or antiretroviral monotherapy should be reevaluated, and signs of treatment failure should precipitate a change in therapy. Thus, an individual currently taking a double-NRTI combination with undetectable plasma HIV RNA level could be safely followed up. One in whom the plasma HIV RNA level is greater than 5000 to 10 000 copies/mL should be considered a virological failure, and alternative treatment should be instituted. For those who fall into an intermediate category of plasma viral load (eg, 400-5000 copies/mL), a confirmed rising viral load should prompt consideration of changing therapy; a stable concentration in this range should prompt careful observation over several months until a trend becomes apparent. Once virological failure occurs, changing therapy while the plasma HIV RNA level is relatively low or moderate may limit the degree of antiretroviral resistance so that a new regimen will have a greater chance of reducing viral load to below limits of detection. This must be balanced against future available drug options.

In addition to the above considerations, a current question is whether patients who are doing well on their current antiretroviral regimen with plasma HIV RNA levels below the limit of detection should have an additional drug added. This approach, which has been termed treatment "intensification," is under study to assess its ability to prolong the benefit of an existing regimen, but it is premature to make any recommendations in this regard.

What To Change To

As stated in the original report, there are a number of factors to consider once a decision has been made to change a therapeutic regimen. These include the primary reasons for changing (eg, failure, nonadherence, intolerance, or toxic effects), antiretroviral treatment history, available options, potential for cross-resistance, comorbid conditions, potential drug interactions, access, and cost. In the case of treatment failure, the guiding principle should be to try to change all drugs in the regimen or at least to include a minimum of 2 new drugs in the revised regimen. The practice of adding a single drug to a prior insufficiently suppressive regimen is strongly discouraged. This approach can be considered to be equivalent to sequential monotherapy, which will lead to more rapid emergence of resistance. Illustrative examples of alternative regimens for patients failing 3-drug regimens are listed in Table 4. Table 5 provides options for patients who are deemed to be failing double-NRTI regimens. Although 4-drug regimens (eg, ritonavir-saquinavir-stavudine-lamivudine) are currently in early clinical trials, it is not yet known whether benefits of such regimens will justify the predictable increases in toxic effects and problems with adherence to the more complex regimens.

When changing because of nonadherence and the concern that viral resistance might occur, the individual reasons for nonadherence must be explored. For example, if the nonadherence is because of low-grade toxic effects, modification in 1 component of the regimen may rectify the situation. If complexities of the regimen (eg, number of pills or dosing schedule) or psychosocial factors are the root cause, a simpler regimen, even though it may carry less than maximal potency, may be more appropriate and, in the long term, more effective.

If change is prompted by drug toxicity early in the course of therapy within an otherwise efficacious regimen and the offending drug can be identified, substituting 1 new drug for the drug responsible for the toxic effect is an appropriate approach. For example, an individual with a viral load below the limit of detection who has a hematologic toxic effect while taking the combination of zidovudine, lamivudine, and indinavir might benefit from replacement of zidovudine with stavudine.

SPECIAL CONSIDERATIONS

Primary Infection

Acute (primary) HIV infection hypothetically represents an opportunity to eradicate HIV from the host, if this is going to be possible. Such treatment would need to be aggressive and initiated as soon as possible after infection occurs. Since cases of acute infection are infrequently diagnosed, and it is not known whether eradication is possible, it is important that such individuals be identified and recruited into ongoing clinical trials whenever possible.

If a clinical trial is unavailable or is declined by the patient, a treatment regimen that includes 2 NRTIs with a potent protease inhibitor is recommended. Such a regimen should be maintained well past the time taken to achieve an undetectable plasma viral load and continued indefinitely, pending new data. Whether it is possible to discontinue such therapy after a prolonged period of adequate suppression is the subject of ongoing trials. During primary infection, some individuals will have been infected with a viral mutant that is resistant to 1 or more antiretroviral drugs. This may lead to an inadequate response to the antiretroviral regimen. Management in this setting should follow recommendations for treatment failure in established infection.

Postexposure Prophylaxis

Existing guidelines for high-risk occupational or accidental exposures to HIV should be followed.[1,55] Treatment should be individualized for each patient, particularly with regard to treatment history of the source patient, if known. Antiretroviral prophylaxis for high-risk sexual exposures is an area of increasing concern. The Centers for Disease Control and Prevention (CDC) is in the process of developing recommendations for postexposure prophylaxis in this setting; that report may be available soon.

Limited information on safety and tolerability of antiretroviral drugs used as postexposure prophylaxis in uninfected persons is a major impediment to developing recommendations. To assist in filling this information gap, health care providers in the United States are encouraged to enroll all workers who receive chemoprophylaxis after occupational HIV exposure in a registry (without personal identifiers) cosponsored by the CDC and several pharmaceutical companies (The toll-free telephone number is [888] PEP-4HIV, ie, [888] 737-4448.)

Perinatal Transmission

The use of antiretroviral drugs for the prevention of perinatal HIV transmission should always be considered in the context of optimal health care for the mother. When indicated for the health of the mother, appropriate antiretroviral therapy should not be withheld because of the pregnancy. Many pregnant women are taking combinations of antiretroviral drugs that have reduced their plasma viral load below detection limits. This approach may prove optimal for the mother as well as the fetus. The management of antiretroviral therapy during pregnancy is, however, complex, and there are scant safety data and no controlled efficacy data for combination antiretroviral therapy during pregnancy. Therefore, no specific recommendations can be made in this regard. For women who are already taking combination regimens and who become pregnant, continuation of the regimen should be encouraged. It is crucial that antiretroviral therapy during pregnancy be initiated or continued only after full discussion between the patient and her physician with regard to the benefits and the potential risks of antiretroviral therapy. For a more detailed discussion of current considerations for antiretroviral therapy in pregnancy, the recent US Department of Health and Human Services report can be consulted.[56]

Zidovudine prophylaxis continues to be recommended for prevention of perinatal transmission of HIV. The regimen of antenatal, intrapartum, and neonatal zidovudine has consistently resulted in reductions of 65% to 75%[56-61] with no immediate serious consequences to the mother, infant, or child development during the first 2 years of life. Zidovudine significantly decreases the likelihood of vertical transmission at all observed levels of maternal HIV viral load.[60]

Since no other antiretroviral drug has yet been demonstrated to significantly reduce the likelihood of vertical HIV transmission, zidovudine should be included as a component of any antiretroviral regimen used during pregnancy whenever possible.

Because of the dearth of information on use of antiretroviral drugs other than zidovudine during pregnancy, all women who choose to take antiretroviral drugs during pregnancy should be encouraged to enroll in the Antiretroviral Pregnancy Registry managed by several pharmaceutical companies in conjunction with the CDC and the National Institutes of Health (telephone number: [800] 722-9292, ext 38465).

SUMMARY

Recent data have provided strong support for the principle that HIV viral replication should be suppressed as fully as possible throughout the course of HIV infection. The field of antiretroviral therapy is a rapidly moving one, and we anticipate that further updates will be forthcoming.

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