Evaluation of New Anti-Infective Drugs for the Treatment of Infection with Human Immunodeficiency Virus

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This guideline describes the preclinical documentation required for a new drug active against human immunodeficiency virus (HIV) and offers suggestions regarding the design and implementation of phase 1, 2, and 3 clinical trials. Drugs with a low level of potential toxicity, especially those that are not nucleoside analogues, should be evaluated in healthy individuals who are not infected with HIV before trials in HIV-infected patients commence. The guideline also discusses possible clinical and laboratory end points for efficacy and emphasizes the need for careful validation of all laboratory end points used. The approach of the guideline is deliberately general: more specific recommendations would soon become outdated in this field, which is characterized by extremely rapid developments.

I. INTRODUCTION

This is one of a series of disease-specific guidelines that have been prepared to assist sponsors and investigators in the development, conduct, and analysis of studies of new anti-infective drugs. This guideline deals with the conduct of phase 1 through phase 4 clinical trials and is a subset of the General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products and of the European Guidelines for the Clinical Evaluation of Anti-Infective Drug Products [1], which should be consulted for the prerequisites to the conduct of studies in humans.

This guideline is intended to be used for the evaluation of drugs designed to act specifically or nonspecifically against human immunodeficiency virus (HIV) but not for the evaluation of drugs used for the treatment of opportunistic infections developing during HIV infection. Lack of coverage in this specific guideline of issues covered by the General Guidelines does not imply that these issues are unimportant [1].

A. General Characteristics of HIV Infection

1. Background

AIDS was first recognized in 1981. Since HIV was identified as the causative agent in 1984 and 1985, the epidemiology and natural history of the infection as well as the biological characteristics of the virus itself have been extensively studied, and a large amount of knowledge about a new disease and its cause has been accumulated with unparalleled speed [2].

HIV, as a member of the retrovirus group, is an RNA virus with an envelope. Through reverse transcriptase (RT), viral RNA is translated into DNA that can be incorporated into the genome of the host cell, an event resulting in chronic infection. Like other retroviruses, HIV is highly variable, especially in terms of its envelope antigens. In fact, each HIV-infected individual harbors several different variants of HIV soon after acquisition of the primary infection. Two distinct types of HIV have been identified: HIV-1, which is the type commonly found in most parts of the world, and HIV-2, which is found predominantly in West Africa. The RNAs of HIV-1 and HIV-2 are different; the RNA of HIV-2 is more like that of simian immunodeficiency virus (SIV) than like that of HIV-1. Nevertheless, the clinical manifestations of infections with HIV-1 and HIV-2 seem to be virtually identical.

The life cycle of HIV includes several well-defined stages, each of which is a possible target for therapeutic intervention. These stages include: (1) adsorption, which requires the attachment of the gp120 antigen of the viral envelope to the CD4 receptor of the host's T lymphocytes, macrophages, CNS cells, and various other cells; (2) fusion, i.e., the integration between gp120 and the cytoplasmic membrane of the host cell; (3) protein uncoating, i.e., the stripping of the outer layer of the virion in order to release viral RNA into the cytoplasm; (4) transcription of viral RNA to DNA by RT, a process that is specific to retroviruses mediated by the virus-encoded RT; (5) integration of proviral DNA into the host-cell genome, which allows the establishment of chronic infection; (6) transcription of proviral DNA to RNA, which
permits the production of new viral RNA; (7) synthesis of viral proteins and glycosylation; and (8) assembly of new virions and their release through budding in the host-cell cytoplasmic membrane. The new infectious virions are finally released from the cell and can infect new cells.

2. Transmission

HIV is transmitted in three ways: by unprotected sexual contact, by exposure to infected blood or blood products, and by vertical exposure of a fetus to an infected mother. The groups at high risk have been defined by these modes of transmission. At the beginning of the AIDS epidemic, the predominant risk group consisted of homosexual and bisexual men; the main routes of transmission were anal and oral intercourse. Later, when the AIDS epidemic in Africa, Latin America, and Asia became apparent, heterosexual intercourse was found to be an important—if not the most important—route of transmission. The risk of such transmission was increased by concomitant ulcerative infections with sexually transmitted agents, such as chancroid and genital herpes simplex. Infection is transmitted via blood or blood products among intravenous drug users who share syringes and needles. Transmission by blood has also been reported from countries in which disposable syringes and needles are not routinely used for health care. The use of blood or blood products from donors not screened for antibodies to HIV constitutes a risk for transmission of infection. This risk has been largely eliminated in Western Europe and the United States but still exists in some developing countries. The risk of accidental transmission of HIV by needle sticks or similar routes seems to be limited (<0.5%) and is far lower than the risk of transmission of hepatitis B virus by the same route. The rate of vertical transmission from an HIV-positive mother to her child ranges from 15% to >30%. This risk appears to be higher in developing countries than in Europe and the United States. Transmission seems to take place shortly before or during delivery. The virus may even be transmitted through the mother’s milk.

3. Natural History

Three distinct stages of HIV infection have been identified.

(a) Acute HIV Infection

Acute infection, with onset 2–4 weeks after primary infection, is documented in ~15% of HIV-infected individuals and is characterized by fever, lymphadenopathy, and—in many cases—tonsillitis and rash. This syndrome is reportedly more frequent among health-care workers, whose infections tend to be sought and detected early on, than among persons whose infections are acquired under less well-defined conditions and generally become apparent at a later stage. It may be that in the latter instance this clinically rather benign condition does develop but is not recalled in retrospect. Acute HIV infection is transient and is characterized by viremia. The patient recovers, and the next stage—asymptomatic infection—begins.

(b) Asymptomatic HIV Infection

The asymptomatic stage lasts for a variable period. The patient is chronically infected but has no clinical symptoms. Surrogate markers are often used to follow the inevitable but temporally variable progression from asymptomatic to symptomatic infection. HIV is isolated from white blood cells and in some cases from plasma as well.

(c) Symptomatic HIV Infection

During this final stage, the host’s immune response is sufficiently impaired to allow opportunistic infections and/or malignancies to develop. The Centers for Disease Control and Prevention (CDC) has recently expanded its surveillance case definition of AIDS ([3], reprinted at the end of this guideline). As of January 1993, the CDC definition of AIDS differs from that used in Europe and that used by the World Health Organization; specifically, a low CD4+ lymphocyte count is an AIDS-defining event only according to the CDC definition. The term AIDS-related complex (ARC) has been used to describe the condition of patients who do not have AIDS but whose clinical picture indicates a serious impairment of the immune response as a consequence of HIV infection. Other infections may be seen in the symptomatic HIV-infected patient that do not fulfill the definition of either AIDS or ARC but clearly indicate a progression of the infection beyond the asymptomatic stage.

B. Therapy for HIV Infection

1. Specific Anti-HIV Drugs

Despite the brief time since the discovery of AIDS and the identification and characterization of the causative agent, a large number of drugs active against HIV have been developed; among these agents, zidovudine (azidothymidine) has been particularly important. As the various stages in the life cycle of HIV have been elucidated, a number of therapeutic options have been investigated. (For continuous updating on the development of new anti-HIV drugs, see the AIDS/HIV Treatment Directory, American Foundation for AIDS Research, New York.)
Efforts have been made to competitively block the adsorption of HIV to the CD4 receptor by administering recombinant CD4 (rCD4) in a soluble form. Studies in humans have not shown rCD4 to be clinically efficacious. Another approach has been to use synthetic CD4 inhibitors, such as aurintricarboxylic acid, sulfated polysaccharides, heparin, dextran polysulfate, pentosan polysulfate, and synthetic peptide T. All of these inhibitors have been associated with problems: they seem to be less active in vivo than in vitro, they are very poorly absorbed from the gastrointestinal tract after oral administration, and some of them may cause severe complications (e.g., bleeding diathesis) if administered intravenously. The CD4 receptor as a target for anti-HIV therapy has also been examined in studies using a synthesized peptide chain identified as the site that binds to gp120. The peptide chain is conjugated with toxic products such as ricin or Pseudomonas exotoxin. Theoretically, such a conjugate would recognize cells expressing gp120 (chronically HIV-infected cells) and kill such cells by toxic activity.

The substructure of gp120 responsible for fusion of the virus to the host cell is a loop on the antigen called the V3 loop. Studies with chimpanzees have shown that, if this loop is blocked by specific antibody, HIV infection is not possible. The gene coding for the V3 loop is highly variable, but the tip of the loop is well conserved. For example, ~90% of all HIV isolates from patients in the United States and ~50% of all those from African patients have a G-P-G-R amino-acid sequence at the tip. Thus, an antibody specifically recognizing the tip amino acids might effectively neutralize HIV.

Nucleoside analogues are compounds that, when incorporated into a newly synthesized RNA or DNA molecule, act as chain terminators and block further synthesis of nucleic acid. In addition, they can compete with intracellular nucleoside triphosphates and act as competitive inhibitors of RT. All nucleoside analogues must be triphosphorylated in the cell to be active. Thus nucleoside analogues are prodrugs that are inactive until triphosphorylation is complete. The search for nucleoside analogues active against HIV has focused on compounds with a high affinity for RT and a low affinity for human DNA polymerase. The higher the ratio, the more likely it is that the DNA synthesis of normal cells will not be inhibited and that cytotoxic adverse reactions will be avoided. The first nucleoside analogue to be developed for clinical use in HIV infection was zidovudine. Later, dideoxynosine (ddI, didanosine) and dideoxycytidine (ddC) were extensively evaluated. Other nucleoside analogues are still being developed.

Extensive clinical trials of zidovudine, ddI, and ddC have shown that this group of drugs has severe limitations. First, these agents do not inhibit viral replication completely; the virus is still isolated from most patients during treatment. Second, resistance to zidovudine is common, especially in cases of advanced disease with enhanced HIV replication. It is likely that resistance to other nucleoside analogues will emerge as well. Third, toxicity is often a limiting factor. Zidovudine mainly causes bone marrow toxicity, while ddI and ddC cause neurotoxicity; ddI also causes severe acute hemorrhagic pancreatitis. A clear relation has been documented between a lack of efficacy of zidovudine and the in vitro emergence of resistance to the drug.

When the nucleoside analogues are compared, ddC seems less effective than zidovudine as single-drug therapy. Limited clinical data indicate that the combination of two nucleoside analogues may be more effective than a single drug. Resistance to one nucleoside analogue does not appear to be indicative of cross-resistance; rather, susceptibility to other nucleoside analogues may be maintained.

Compounds that are not nucleoside analogues but that nevertheless inhibit RT in vitro have been discovered. Their mode of action remains to be clarified; although they are active against HIV-1, they have no activity against HIV-2 or SIV and are easily rendered ineffective through single mutations. Early clinical trials have determined that the latter problem may seriously reduce the usefulness of these drugs as monotherapy for HIV infection.

DNA-to-RNA transcription can be inhibited in vitro by so-called antisense oligonucleotides or hybridones. These synthetic nucleotides are complementary to defined sequences in the viral genome. An example is the tat gene, which up-regulates viral gene expression. A shortcoming of these compounds is their susceptibility to cellular nucleases.

Specific proteases catalyze the formation of new viral proteins in host cells by cleaving precursor proteins produced by the infected cells. Several polypeptides have been synthesized and have shown in vitro activity. A few drugs that block the glycosylation of viral proteins in vitro have also been synthesized. However, such drugs do not seem to distinguish between viral and host-cell enzymes. In addition, a low level of bioavailability after oral administration and rapid metabolism limits the potential usefulness of these drugs.
(g) Assembly and Release of New HIV Particles
As of the end of 1991, only one drug interfering with viral-particle assembly and release had been synthesized. This drug, which was designated hypericin, inhibits protein kinase in vitro [4].

2. Immunostimulants
The above-described approaches to therapy for HIV infection have all been designed to interfere directly with viral replication. Another approach is to strengthen host’s defense by any of several means—specific or nonspecific.

(a) Interferon
Interferon is a cytokine with immunostimulating properties as well as antiviral activity. Trials with interferon-α and leukocyte interferon have been ongoing for several years. Both of these interferons have been used alone and in combination with other anti-HIV drugs, mainly zidovudine. In some instances treatment has resulted in a decrease in levels of the virus and of p24 antigen in plasma. However, a high frequency of severe adverse reactions has limited the usefulness of leukocyte interferon when it is administered with zidovudine to patients with end-stage AIDS.

(b) Synthetic RNA
Synthetic mismatched RNA functions as a potent nonspecific immunostimulant. The therapeutic efficacy of such compounds in HIV-infected patients remains to be proven.

(c) Immunostimulants with Unknown Activity
Of the several compounds tested, some (e.g., isoprenosine) may delay the progression of asymptomatic HIV infection to AIDS.

3. Passive and Active Immunotherapy
Investigations are presently being conducted on changing the course of HIV infection by administration of antibodies to HIV antigens or by active immunization (vaccination) against such antigens. Special guidelines for documentation of the safety and efficacy of these products must be developed.

(a) Monoclonal Antibodies
Monoclonal antibodies to structures in the HIV particle could theoretically prevent the dissemination of HIV infection from chronically infected cells. The main problem with this approach is the high degree of variability of HIV antigens.

(b) Vaccination
Vaccination with various antigens or with combinations of antigens is being investigated in animal models and in early clinical trials.

4. Combination Treatment
As in therapy for cancer, future regimens for the treatment of HIV infection will probably include combinations of drugs with or without immunotherapy. Several drugs with anti-HIV activity have proven synergistic in vitro.

II. INFORMATION NEEDED BEFORE CONDUCTING CLINICAL TRIALS
A. General Aspects
The epidemiological characteristics of the HIV epidemic and the lack of a specific treatment that eliminates the infection or permanently inhibits its progression have led to an urgent need for new therapeutic entities. To some extent, this need has resulted in less thorough preclinical documentation than has been required for other new anti-infective drugs. Clearly, however, the more information obtained before clinical trials are started, the easier it will be to design such trials properly and to avoid unnecessary errors. The extent of toxicologic documentation may need to be increased if a drug is intended for trials including asymptomatic HIV-infected patients.

B. In Vitro and in Vivo Preclinical Documentation of Efficacy
1. Specific Anti-HIV Drugs
Drugs presumed to act on the replication of HIV should be tested in vitro. Documentation of their effects should include identification of the site of their activity, i.e., the stage of the viral life cycle that they affect. Quantitative data on anti-HIV activity should be compared with the results obtained when currently approved drugs are used as controls. Since there is no standard definition of anti-HIV activity, the methods used must be described in detail and validated. In vitro documentation should include studies of the emergence of resistance to the compound studied and of the agent’s synergistic, additive, or antagonistic effects in combination with other anti-HIV drugs. The strains of HIV used should be described; several strains should be tested, at least one of which is a well-known reference strain. The cell culture systems used should be described, and, at a minimum, lymphocytes expressing CD4, monocytic cells, and peripheral-blood lym-
phocytes should be used. In vitro evaluations should include studies of the synergy of anti-HIV drugs.

Documentation of specific in vivo activity against HIV-1 (e.g., that of non-nucleoside inhibitors of RT) is difficult since chimpanzees are the only experimental animals susceptible to this virus. For drugs with general antiretroviral activity, monkeys infected with SIV can be used for documentation of in vivo activity and for preclinical documentation of the kinetic properties of a compound. Such investigations should include studies on penetration into extravascular compartments and on intracellular concentrations.

2. Immunostimulants

Since the activity of immunostimulants on HIV infection is indirect, their in vitro activity is often difficult to study. Thus the demands for in vitro documentation must be adapted to the properties of each individual compound.

Studies of animals infected with a retrovirus should be undertaken; whenever possible, this virus should be one that causes an immunodeficiency syndrome, e.g., SIV in primates or perhaps HIV in severe combined immunodeficiency disease (SCID) mice. At present, however, such studies are not required by regulatory agencies.

C. In Vitro and in Vivo Preclinical Documentation of Safety

Preclinical studies on in vitro and in vivo toxicity should be undertaken for all anti-HIV drugs. The minimal requirements are that toxicity in cell culture is documented in vitro and that subacute toxicity (lasting for ≥2 weeks) is documented in at least two animal species (one rodent and one nonrodent) before clinical trials are started. In light of the need for rapid development of new anti-HIV drugs and (apparently) for lifelong specific treatment of HIV infection, data from long-term toxicity studies, including studies on carcinogenic properties, should not necessarily be required before clinical trials involving patients with symptomatic HIV infection are started. Such toxicity studies can continue to be reported during the course of a drug's development. Data on teratogenicity should be available before trials including fertile women are begun.

III. QUALIFICATIONS OF INVESTIGATORS AND INSTITUTIONS

A. General Aspects

See General Guidelines [1], section VII.

B. Specific Aspects

All centers involved in clinical trials of therapy for HIV infection should have access to laboratories using well-validated methods for the following investigations: (1) quantitative analysis of T lymphocyte subsets, including determinations of CD4+ and CD8+ T lymphocytes; (2) HIV antibody testing, with access to screening methods and to techniques for confirmation of HIV antibody positivity; (3) testing for other surrogate markers, including β2-microglobulin, neopterin, and routine hematologic markers; and (4) diagnostic tests for opportunistic infections. Each center must be able to diagnose the most common opportunistic infections among HIV-infected patients, including Pneumocystis carinii pneumonia, Toxoplasma gondii encephalitis, Candida albicans esophagitis, Cryptococcus neoformans meningitis, mycobacterial infections, herpes simplex infection, and cytomegalovirus esophagitis and retinitis. All such diagnoses should be confirmed by clinical, microbiological, and radiological procedures.

The centers undertaking studies, especially those performed in phase 1 and phase 2 trials, may require access to relatively sophisticated virological laboratory services, such as methods for the assay of acid-hydrolysis p24 antigen, techniques for the isolation and quantitation of HIV in whole blood and plasma, and the quantitative RNA polymerase chain reaction (PCR). Requirements for standardization (within and between centers) and for validation of methods should be carefully described in the study protocol.

IV. DESIGN AND IMPLEMENTATION OF PHASE 1, 2, AND 3 CLINICAL TRIALS

See General Guidelines [1], section III.

A. Phase 1 Trials

Depending on the potential toxicity of the drug studied, phase 1 studies may include healthy, non-HIV-infected individuals; asymptomatic HIV-infected patients; and/or patients with symptomatic HIV infection. When preclinical studies indicate a low level of potential toxicity, a drug may be evaluated for pharmacokinetic properties in healthy, uninfected persons; thus the problem of handling HIV-infected samples will be avoided. Such trials should include measurements of intracellular drug concentrations. Dose ranges and the efficacy of single-dose vs. multiple-dose regimens should be assessed in phase 1 trials, and the results should serve as a basis for selection of the dosages used in phase 2 and phase 3 trials. Dose-ranging studies in various stages of HIV infection may be needed; if so, they should include nonclinical end points, such as quantitative viremia, kinetics of active metabolites, and extravascular distribution of active compound. Phase 2 studies should also include an evaluation of possible interactions with other drugs—both those specifically active against HIV and those commonly administered to HIV-infected patients for other indications. The latter studies are
especially important for drugs that depend on the cytochrome p450 system for liver metabolism.

When drugs with the potential for a high degree of toxicity (e.g., nucleoside analogues) are tested, phase 1 studies should normally involve HIV-infected patients. The specific group(s) studied should depend on the degree of expected toxicity; for the potentially most toxic compounds, participants in the trial should have AIDS. Some phase 1 studies, especially those that include the assessment of dose ranges and multiple-dose pharmacokinetics, may include measurements of therapeutic efficacy and in fact, therefore, may have both phase 1 and phase 2 components.

B. Phase 2 and Phase 3 Trials

1. Selection of Patients

Inclusion and exclusion criteria should be defined in detail in the protocol. Potential criteria for inclusion are (1) age and sex and (2) stage of HIV infection, assessed according to classification systems, surrogate markers, and clinical symptoms. The latter criterion is important since anti-HIV drugs, especially nucleoside analogues, seem to be more toxic for patients with advanced HIV disease than for those who are asymptomatic or minimally symptomatic. With regard to the former criterion, the increasing frequency of HIV infection among women and children makes the inclusion of these groups in phase 2 and phase 3 trials worthy of consideration.

Exclusion criteria vary from trial to trial and also depend on the type of drug studied and its toxicity. In phase 2 trials, many individuals are usually excluded in an effort to obtain a well-defined sample of patients. In contrast, phase 3 trials should be as inclusive as possible so that the results reflect a representative population of patients. One exclusion criterion that should be considered in studies of anti-HIV drugs is previous and/or concomitant treatment with other agents. In all trials, pregnant and nursing women should be carefully considered for inclusion.

2. Design of the Trial

In general, studies of anti-HIV drugs should be comparative. Noncomparative studies may be performed in the early stages of phase 2 trials. However, because of the progress made in the treatment of opportunistic infections, historical controls are not considered reliable for the assessment of clinical efficacy. The use of placebo controls is rarely justified in trials involving patients with symptomatic HIV infection since several drugs have proven to be efficacious. In studies of asymptomatic infections (especially those among patients with CD4 lymphocyte counts of >500/mm³) and in studies of postexposure prophylaxis, the use of placebo controls may be considered unless effective treatment has been documented.

If possible, trials should be blinded. A double-blind design may be difficult to implement because of varied routes of administration or characteristic adverse effects of one of the compounds. In such cases an evaluator-blinded design should be used; i.e., the results should be evaluated by an independent person who is unaware of the treatment given.

3. Sample Size

See General Guidelines [1], section XVI.F.

4. Randomization and Stratification

See General Guidelines [1], sections XI.B and XI.C. Prospective stratification should be used for participating centers. If few vital prognostic factors can be identified (for example, the stage of HIV infection, the age of the patient, and the previous anti-HIV treatment administered), prospective stratification for such factors can be undertaken. However, no more than three stratifying factors should be used. Even if an imbalance between groups is suspected with regard to the proportions of patients with a certain risk factor, the problem can be rectified by post-stratification at the time of analysis.

5. End Points for Efficacy

Deciding on the end points to be used in a trial of an anti-HIV drug is crucial. So far, no relevant guidelines have been published by regulatory agencies. On the basis of the natural history of HIV infection and the various stages of the disease, the following end points can be considered.

(a) Death

Death, although a highly objective end point, is difficult to apply even in studies of patients with advanced AIDS. Although useful in the drawing of conclusions from early trials of zidovudine, death as an end point is more likely today to result in the prolongation of a study of anti-HIV drugs. In most cases, therefore, it should not be the primary end point.

(b) Opportunistic AIDS-Defining Events

Opportunistic infections and malignancies, along with other opportunistic AIDS-defining events, are recommended as end points, whether or not the patients involved have AIDS at enrollment. Both the type and the number of such events as well as the time when the first event takes place should be analyzed. Efforts should be made to differentiate novel events from recurring events. Each event and the procedures required for its diagnosis should be described in detail in the trial’s protocol. Efforts should be made to standardize prophylaxis for opportunistic infections, and all such
prophylaxis administered should be documented for each patient.

(c) Clinical Manifestations of HIV Infection Per Se

CNS manifestations of HIV infection constitute an AIDS-defining event. Their demonstration requires fairly extensive neurological and neuroradiological examinations, which should be defined in the protocol. Normally this end point is used in combination with AIDS-defining opportunistic infections and malignancies (see [3], Appendix B; reprinted at the end of this guideline).

(d) Non-AIDS-Defining Opportunistic Events

Examples of non-AIDS-defining opportunistic events are oral candidiasis (microbiologically documented), herpes zoster (microbiologically or photographically documented), and diarrhea and hairy leukoplakia (photographically documented). Each event and the procedures required for its diagnosis should be described in detail in the protocol. Details on definitive and presumptive diagnoses need to be provided.

(e) Viremia

The use of viremia as an end point has increased with the advent of improved techniques for its demonstration and quantitation. Viremia can be demonstrated by culture of whole blood or plasma or by RNA PCR. If possible, the technique used should be quantitative. Clearly, present techniques are too laborious to permit an investigation of all the patients included in a phase 3 trial. In phase 2 trials, however, quantitative virological studies may allow a rapid evaluation of the anti-HIV effect of a new drug. The techniques must be carefully described and validated for each center in the protocol. One central laboratory for studies of viremia should be used whenever possible. The acquisition of resistance should be evaluated by simultaneous testing of samples taken before, during, and after treatment.

(f) CD4+ Lymphocyte Counts

The absolute and relative numbers of CD4+ T lymphocytes have a clear prognostic value, as does the rate of decline in these numbers. CD4+ counts of <200/mm³ have been accepted as an AIDS-defining event by the CDC (but not by similar European organizations or the World Health Organization). The difficulties encountered in determining CD4+ lymphocyte counts are due to variations in intraassay and interassay reproducibility and in the individual patient. If CD4+ lymphocyte counts are employed as an end point in a clinical trial, the technique used for determinations must be carefully standardized and validated. It is recommended that both absolute CD4+ counts and CD4+-to-CD8+ ratios be calculated. The results of single determinations should not generally be accepted as indicators of progression or regression of the disease. The conditions under which blood samples are obtained from patients should be standardized.

(g) Determinations of p24 Antigen

The presence of p24 (one of the core antigens of the HIV particle) in peripheral blood reflects viremia. However, several studies have failed to show a correlation between p24 antigenemia and clinical progression. It therefore seems unreliable to use p24 antigenemia as an end point in a clinical trial, although it can be used as an indicator of antiviral activity.

(h) Other Surrogate Markers

Other laboratory tests often used to predict or follow the clinical progression of an HIV infection are β2 microglobulin and neopterin (an acute-phase reactant) in serum. In the future, cytokines are likely to be used as well. So far, clear and reproducible correlations between clinical progression and such surrogate markers in the individual patient have not been demonstrated. All laboratory techniques must be validated.

(i) Quality of Life

Since some of the drugs used for the treatment of HIV infection are cytotoxic or have marked adverse effects, they may negatively impact the patient’s quality of life. Methods for evaluating the quality of life during treatment should be developed; results of such evaluations may be considered secondary end points.

C. Analysis of Efficacy

See General Guidelines [1], section XIII.

D. Methods of Assuring Compliance

Compliance has been a problem in many trials of treatment for HIV infection, especially those that have used placebo controls. The study design should incorporate procedures for the assessment of compliance, including conventional methods (such as pill counts and interviews with patients) and, if possible, more objective techniques (in particular, assays for the study drug and other anti-HIV drugs in urine or plasma).
E. Methods of Assessing Safety

See General Guidelines [1], section XIV. Since many anti-HIV drugs are new chemical entities, no similar drugs have previously been administered to humans. It is thus important to register adverse events even if they are not obviously related to treatment. The important factor is then to find any differences between the drugs tested rather than to detect true frequencies of an event. The analysis of adverse laboratory events may be confounded by laboratory abnormalities caused by opportunistic infections or by HIV infection itself. However, comparisons between groups may reveal unexpected events. Adverse events should be carefully analyzed in relation to the dosages administered.

F. Good Clinical Practice

In trials involving HIV-infected patients, an unconventional design may compromise strict adherence to the standards of good clinical practice. Such trials often are sponsored not by pharmaceutical companies but rather by scientific organizations and investigators who lack the specific expertise and experience that is indispensable in executing large-scale clinical trials. Clinical trials of anti-HIV drugs must be designed in a way guaranteeing that normal standards of good clinical practice are maintained. A Data and Safety Monitoring Committee should be appointed for each trial and involved in monitoring the strict adherence of these trials to sound standards.

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References