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GLOBAL PROGRAMME ON AIDS AND TRADITIONAL MEDICINE PROGRAMME

Report of a WHO Consultation on Traditional Medicine and AIDS: Clinical Evaluation of Traditional Medicines and Natural Products

Geneva, 26-28 September 1990

CONTENTS

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection and the consequent acquired immunodeficiency syndrome (AIDS) pose an unprecedented challenge to health planners, clinicians, other health workers, scientists and the community at large. The World Health Organization (WHO) currently estimates that more than 8 million people are already infected with HIV and about 1 million adults have suffered or are suffering from AIDS.

Persons with AIDS are seeking many different treatments, some using plant products, with the hope of obtaining either a cure or relief of symptoms. There is scientific evidence, based on *in vitro* studies, that some medicinal plants do in fact have inhibitory effects on HIV. A consultation on *in vitro* screening of traditional medicines for anti-HIV activity, held in Geneva from 6 to 8 February 1989, offered promise that scientifically valid collaborative studies of traditional medicines, particularly medicinal plants, might lead to effective and affordable therapeutic agents.[1]

Against this background, the Global Programme on AIDS (GPA) Biomedical Research Unit, and the Traditional Medicine Programme (TRM) of the World Health Organization (WHO) convened a consultation in Geneva from 26 to 28 September 1990, with the objective of developing guidelines on the clinical evaluation of the safety and possible efficacy of traditional remedies in the treatment of persons with AIDS.

The consultation was attended by ten participants from eight countries (Annex 1). Opening the meeting, Dr Hu Ching-Li, Assistant Director-General of WHO, cited the growing menace posed by AIDS and emphasized the limitations of existing drug therapy. Traditional medicines, which are being used empirically in many countries for the treatment of AIDS, therefore need to be evaluated clinically to establish their safety and possible efficacy in the treatment of AIDS and AIDS-related diseases.

Dr O. Akerele, Programme Manager, TRM, outlined the activities of the programme with particular reference to the collaborative activities with GPA.

Dr J. Esparza, Acting Chief, Vaccine Development, GPA, welcomed the participants on behalf of GPA and provided information on the general goals and current activities of the programme.

2. BACKGROUND INFORMATION

2.1 Traditional medicine products used in HIV infection and disease

Several countries have traditional medicine products that are used in the treatment of HIV infection and to ameliorate symptoms and prolong the life of persons with AIDS.

In vitro anti-HIV activity has been reported for the following Chinese medicinal plants: *Glycyrrhiza uralensis, Hypericum perforatum, Viola yedoensis, Alternanthera philoxeroides, Andrographis paniculata, Arctium lappa, Lithospermum erythrorhizon, Coptis chinensis, Epimedium grandiflorum, Lonicera japonica* and *Prunella vulgaris*.

The protein trichosanthin (compound Q or GLQ 223), isolated from the Chinese herb *Trichosanthes kirilowii*, has been used not only in China as an abortifacient, but also to treat patients with AIDS in unofficial trials in the United States of America. Compound Q has also been approved for limited clinical trial by the United States Food and Drug Administration. It has been reported to interfere with the replication of HIV, and selectively to eliminate infected cells.

Kampo is a pharmacotherapeutic branch of Oriental medicine that originated in ancient China and is still being used today in Japan. Originally Kampo medicines consisted of a variety of crude drugs prepared in several hundred different combinations as decoctions, powders or pills. Today, however, the extracts of crude drugs are formulated under strict quality control using state-of-the-art technology. Kampo medicines play a large role in modern medical care in Japan and are expected to continue to do so in future.

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[1] **Bulletin of the World Health Organization**, **67**(6): 613-618 (1989).

One Kampo medicine, **Sho-saiko-to**, has been used to treat a number of different diseases, including viral hepatitis. It has been reported that **Sho-saiko-to** (which contains glycyrrhizin) has an immunoenhancing effect on the interleukin cascade. Thus, **Sho-saiko-to** might have potential for use in the treatment of some phases of HIV infection. This medicine also has anti-inflammatory activity and induces the production of lipocortin, a protein produced by the cell nucleus. This is only one example of a Kampo medicine with pharmacological activities that could be useful in the treatment of persons with AIDS.

2.2 Summary of immunological aspects and considerations

WHO has proposed that the following prognostic categories of the disease should be used in describing the course of HIV infection and disease: (1) asymptomatic/persistent generalized lymphadenopathy; (2) early (mild) disease; (3) intermediate (moderate) disease; and (4) late (severe) disease (AIDS) (see Annex 3). After becoming infected with human immunodeficiency virus type 1 (HIV-1), persons may remain asymptomatic for years before the onset of AIDS. During this asymptomatic phase there may be functional abnormalities of both T-cells and B-cells, even if lymphocyte numbers remain normal. At present, it is not clear whether the immune system abnormalities in either the asymptomatic phase or clinical AIDS are due solely to the direct effects of HIV-1 or whether they also reflect defects existing prior to infection in the host immunoregulatory mechanisms.

One characteristic feature of retrovirus infections is the ability of the virus to insert a DNA copy of its viral RNA genome into the genome of the host cell. During HIV infection, the integrated proviral genome may remain in an inactive state until appropriate activating signals stimulate viral expression. Because of the possibility of induction of HIV expression by T-cell activating factors, such as mitogens and antigens, it is recommended that in clinical trials with traditional medicines with a known immunomodulating effect, antivirals should also be given. On the other hand, the development of humoral and cell-mediated responses against HIV soon after acquisition of infection with HIV clearly demonstrates the ability of the immune system to counteract HIV-1 infection. Immunostimulators might, therefore, also be considered for clinical testing, either alone or together with a specific antiretroviral agent for the treatment of patients in stages of the disease with a small virus burden, e.g., in the asymptomatic phase.[1]

Drugs active against HIV enzymes (e.g., reverse transcriptase inhibitors) may also benefit patients with AIDS. However, screening for anti-HIV activity using single-cell immune cultures may be of only limited value, because the pathogenesis of AIDS involves several types of immune cells and complex relations among the cytokines of the immunological network.

Animal models will play a central role in AIDS research in the coming years. Important models include HIV-infected chimpanzees, immunodeficiency virus-infected simian monkeys, and ungulates and cats with HIV-related lentivirus infections. However, animal models may not exhibit all the features of human HIV infection.

2.3 Current drug-screening activities

Medicinal plants that have been used as anti-infective agents in the prevailing systems of traditional medicine in different geographical areas are being systematically collected in order to evaluate their anti-HIV potential. For this purpose a collaborative project has been established between the WHO Collaborating Centre for Traditional Medicine at the University of Illinois, Chicago, USA, and the WHO Collaborating Centre for AIDS at the National Bacteriological Laboratory in Stockholm, Sweden. The preparation of primary extracts is being coordinated by the Chicago group, and the extracts are then sent to the Stockholm facility for anti-HIV testing *in vitro*. The two centres have so far evaluated 36 extracts representing 18 plant species. Activity has been found in extracts from two species, which are of great interest because of their low toxicity.

The finding of two active species in 18 samples represents a high rate of success. If the initial project goal of collecting 200 samples by the end of 1990 is attained, a projected total of about 11-12 active plant

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[1] Report of a WHO informal consultation in preclinical and clinical aspects of the use of immunomodulators in HIV infection, Geneva, 3-5 April 1989, **AIDS**, **4**(12): WHO1-WHO14.

species can be expected to serve as candidates for bioassay-directed fractionation and eventual isolation of active principles. It is WHO's policy to ensure that the benefits from the development of drugs as a result of collaborative efforts such as this one are, as far as possible, made widely available on an equitable basis.

In addition, bimonthly and annual reports to WHO on anti-HIV active compounds of known structure and natural product extracts having anti-HIV and related activities (e.g., reverse transcriptase inhibition, other enzyme inhibitions, etc.) are provided through a computerized data base, NAPRALERT (Natural Products Alert), established by the WHO Collaborating Centre in Chicago.

The plant-derived chemicals of known structure listed in Table 1 are those reported to date to have anti-HIV activity.

Table 1. Phytochemicals that inhibit HIV *in vitro*[a]

Compound	Compound class
Arabinitol, L: 1,4-dideoxy-1,4-imino:	Carbohydrate
Castanospermine	Indolizidine
Castanospermine, 6-0-Butyryl:	Indolizidine
Colchicine	Alkaloid
Fucitol, L: N-(5-carboxylmethyl-l-pentyl)-1-5-amino:	Carbohydrate
Glycycoumarin	Coumarin
Glycyrrhizin	Triterpene
Glycyrrisoflavone	Flavonoid
Gossypol	Sesquiterpene
Gossypol, (+):	Sesquiterpene
Gossypol, (-):	Sesquiterpene
Hypericin	Quinoid
Hypericin, pseudo:	Quinoid
Licochalcone A	Flavonoid
Licoflavonol, Iso:	Flavonoid
Licopyranocoumarin	Coumarin
Nojirimycin, 1-deoxy:	Carbohydrate
Oenothein B	Tannin
Papaverine	Isoquinoline
Viola yedoensis polysaccharide	Polysaccharide
Prunellin	Polysaccharide
Punicalin	Tannin
Quinic acid, 1,3,4,5-tetra-O-galloyl:	Tannin
Quinic acid, 3,4,5-tri-O-galloyl:	Tannin
Quinic acid, 3,4-di-O-galloyl-5-O-galloyl:	Tannin
Quinic acid, 3,5-di-O-galloyl-4-O-galloyl:	Tannin
Quinic acid, 3-O-digalloyl-4,5-di-O-galloyl:	Tannin
Ricin A Chain	Peptide
Soybean saponin B-1	Triterpene
Soybean saponin B-2	Triterpene
Sulfapatrinoside I	Triterpene
Sulfapatrinoside II	Triterpene
Trichosanthin, alpha: (GLQ223)	Protein

[a] Excludes sulfated polysaccharides.

3. PRECLINICAL CONSIDERATIONS

The participants discussed a variety of issues related to the preclinical stages in the development of traditional medicines and other natural products for the treatment of AIDS. The major points are summarized below.

3.1 Botanical verification

The performance of a clinical trial under controlled conditions requires a constant supply of a product whose botanical identification and characterization can be verified. Lack of assurance of plant species identity is arguably the most serious deficiency of commercial herbal products. If there is no reliable chemical basis for determining identity, and botanical morphology is destroyed during formulation by such processes as powdering and extraction, only **independent botanical certification** can provide the necessary assurance.

A botanical certification scheme, organized along the lines of the WHO certification scheme for pharmaceutical products, would be an invaluable international stimulus towards botanical quality assurance. Each professional grower/supplier of medicinal plant material would be required to submit to the designated national botanical authority an appropriate sample of the plant, in a state of sufficient integrity to allow physical identification for confirmation of species identity. If appropriate, a certificate would then be issued indicating the currently accepted Latin binominal, and synonyms, with associated authority, and its usual common names, as well as the site and date of harvest of the crop. Professional growers could be registered with the national authority and samples for testing could be collected by trained inspectors or qualified botanists. Plant products with established pharmacological activity would be standardized on the basis of correlation of activity with levels of their known active constituent(s) or with appropriate chemical profiles. The products would also be checked for the presence of "characterizing substances", where applicable, for further confirmation of botanical origin. The part(s) of the plant used to make each preparation should be indicated, as well as detailed instructions for harvesting (e.g., stage of growth), storage and processing, prior to and following formulation.

3.2 Pharmacological activity

Before a new drug of known chemical structure is tested in a clinical trial, there must be adequate data from *in vivo* and/or *in vitro* studies to validate its claimed therapeutic efficacy. In the case of known herbal remedies, such evidence may be available from the current practices of traditional health practitioners or from reports in the literature.

Establishing a correlation of pharmacological activity with some component in the plant is an invaluable aid to assuring comparability between preparations of a medicinal plant product. In the case of HIV infection, a number of *in vitro* approaches are available for evaluating antiviral activity. The *in vitro* anti-HIV assay could also lead to a chemical assay for active constituent(s).

3.3 Safety

There are several aspects of safety that need to be considered for herbal products that are candidates for a clinical trial. The first requirement is to identify any potential toxicity by undertaking an extensive search of the literature and evaluating performance in preclinical toxicological tests. The range of preclinical tests available for the evaluation of a synthetic drug before beginning clinical trials is well known. What is not known, however, is whether such preclinical tests need to be so extensive for traditional medicines.

The use of traditional plant remedies over a long period of time may provide important information on the pharmacological effects in humans of a particular group of chemical compounds - information that is usually not available when testing begins on a new synthetic drug. Because herbal remedies have often been used for centuries, their preparation having been described in classical texts of traditional medicine, they cannot be considered "new drugs" in the same sense as new drug candidates from the pharmaceutical industry, which are usually pure and well characterized chemical entities, never before used in humans. Testing requirements formulated by regulatory authorities to ensure the safety of "new drugs" are therefore not necessarily applicable to traditional remedies. A more limited range of preclinical toxicological tests may be adequate for traditional remedies. Consideration must also be given to the cost of performing extensive

animal toxicological tests in developing countries, particularly where laboratory infrastructure is limited. Further, such tests require time that cannot be justified when no other treatment is available. Thus, limited animal testing of a herbal medicine may be justified by the remedy's previous use in human disease and the fatal character of AIDS.

Because of time-tested usage, national drug testing policies may permit some herbal remedies to be submitted directly to clinical evaluation without prior preclinical or toxicological tests. Other remedies may need at least some preclinical toxicological testing. The requirements for testing will be determined for each country, by its own authorities, in the context of its own regulations, and on the basis of pertinent scientific data on the herbal preparation and its history of use in humans.

When a traditional remedy results in promising activity, either in a bioassay or a human study, further investigation may yield a chemically defined active principle, which might then be considered a "new drug" that would have to be tested for safety and efficacy as prescribed by drug regulatory authorities. Such active agents, however, would probably be given special ("fast-track") consideration because of the urgent need for new drugs effective against AIDS.

A second safety consideration is the prompt recognition of any toxic events that may occur during the course of a clinical trial. It may be particularly difficult to recognize toxic events during a clinical trial in persons with AIDS because of the large number of organ systems usually involved in the disease state and the presence of secondary disease/opportunistic infections. Thus, adverse side effects may be masked by the normal progression of AIDS and related diseases and it may be difficult to determine whether a new drug actually accelerates the progress of the disease. It is also possible that the incidence and extent of drug toxicity may be increased in organ systems that are compromised by AIDS or AIDS-related diseases, a problem that even extensive testing in animals may fail to predict.

All patients with AIDS, and particularly those entering clinical trials, must be carefully screened for underlying diseases that may not yet have become clinically important. Such diseases are particularly important when they may compromise either liver or renal function and thus prevent adequate drug elimination. Overall health status must therefore be well characterized at the time that a patient is evaluated for entrance to a study.

Because there is always the possibility of an adverse drug reaction during the testing of a new drug, the study design must include a plan for managing patients who experience some manifestation of drug toxicity. Such problems may be exacerbated in AIDS patients because of their susceptibility to secondary infections, which may require treatment with additional drugs. Additional diseases and the drugs used to treat them increase the likelihood of adverse drug interactions as well as adverse reactions to the drugs themselves. The preclinical plan must address these possibilities.

4. CLINICAL CONSIDERATIONS

Every clinical trial must be conducted according to a protocol that is written and approved before the study starts. The most satisfactory protocols are those that are designed with the collaborative effort of a team of experts representing various disciplines. The trial protocol should include a justification for the trial, and should clearly define the question that the trial is designed to answer. The study population must also be clearly defined, indicating both inclusion and exclusion criteria and the procedures to be used for recruiting study participants and allocating them to various treatment protocols. Study patients should have confirmed HIV infection, either asymptomatic or early symptomatic; in most cases, children and pregnant or lactating women should be excluded. Patients may be recruited from voluntary testing centres and from clinics treating either AIDS or other sexually transmitted diseases. Appropriate informed consent must be obtained from each patient, and each patient should have the opportunity to receive appropriate counselling. The protocol should define appropriate clinical monitoring to detect toxicity as well as to determine efficacy and a plan to deal with drug toxicity should it occur.

An accurate record must be kept for each patient in the study, which should include documentation of informed consent, a medical history, details of treatment received and succinct reports of all physical examinations, follow-up evaluations and laboratory test results.

Efficacy should be judged on the basis of such defined end-points as specific clinical symptoms or signs, the development of particular opportunistic infections, or defined prognostic laboratory markers. Safety should be monitored on the basis of either symptoms or signs, particular attention being given to end-points that may signal forms of toxicity that might be anticipated. Laboratory indicators of liver, renal, cardiac and haematological toxicity should also be monitored.

Evaluation of the trial should be undertaken using appropriate statistics.

Ideally, the study design should be blind, randomized and placebo-controlled. A cross-over design may present problems in interpretation of study results, both because of uncertainty concerning the time course over which a drug may act and because a patient's status may change during the two phases of the study.

Every effort must be made to address the problems concerning preparation, quality control and dose standardization for herbal preparations, and to find a satisfactory placebo.

5. RECOMMENDATIONS

A place for traditional herbal remedies in the health care system will be established only if recommendations for their use are based on studies that make them credible and acceptable. Thus, studies with herbal medicines must satisfy the same criteria of efficacy and safety as do the drugs that are products of the modern pharmaceutical industry.

In this context, the consultation drew up a series of guidelines for clinical trials with traditional medicine products used in the treatment of AIDS and AIDS-related diseases, which are presented in Annex 2.

The consultation also made the following recommendations:

(1) This report should be given wide distribution so that the guidelines can be readily and immediately applied in countries where potential remedies may exist.

(2) The guidelines should be used as the basis for the development of clinical trials for the evaluation of traditional medicines and natural products.

(3) WHO should monitor the impact of the use of the guidelines at the country level to determine any needs for revision.

(4) A second consultation should be convened in two years' time to revise the guidelines on the basis of experience in their use.

(5) The WHO Traditional Medicine Programme, together with the WHO Global Programme on AIDS, should jointly identify appropriate institutions in developing countries where clinical evaluation of traditional medicines and natural products for AIDS could be carried out.

(6) Other consultations should be convened by the WHO Traditional Medicine Programme, in collaboration with appropriate WHO programmes, to adapt the guidelines for the clinical evaluation of traditional medicines for other primary disease states that are of concern in developing countries, such as malaria and other parasitic diseases.

ANNEX 1

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ANNEX 2

GUIDELINES FOR CLINICAL TRIALS WITH TRADITIONAL MEDICINE PRODUCTS USED IN THE TREATMENT OF AIDS AND AIDS-RELATED DISEASES

1. INTRODUCTION

The enormous threat of AIDS to world health requires that all avenues be explored in the search for effective ways of controlling this disease. Recognizing that few therapeutic agents are effective in the treatment of AIDS and that these are often unavailable or too expensive to treat all those afflicted, WHO convened a consultation to determine how to investigate systematically traditional medicines that may have therapeutic benefit for many populations. While it may not be easy to apply current standards of drug evaluation to traditional remedies and natural products, investigation of these remedies may make some contribution to the relief of the current crisis. It is hoped that the guidelines for clinical trials presented below will be applicable under many circumstances and in many locations, and will encourage health care professionals to undertake drug trials that will uncover useful substances for improved treatments of AIDS and AIDS-related diseases. It is also hoped that they will encourage clinical studies that make accurate assessments and can be replicated in different populations.

2. PRECLINICAL CONSIDERATIONS

Clinical trials are expensive and carry some risk to those participating, either from adverse side effects or lack of information on the efficacy of the agent under study. Thus, it is of the utmost importance to identify clearly those approaches and agents that carry the highest potential for success before beginning a clinical trial. Some of the considerations that should be addressed before beginning a clinical trial are discussed below.

2.1 Reasonable assurance of potential human benefit either from prior clinical evidence or *in vitro* test results

There must be some prior evidence of the effectiveness of a potential agent against HIV infection and disease before it can be considered for a clinical trial. Such evidence might be anecdotal, concerning known clinical use, or come from pharmacological screening. Relevant pharmacological activity might include antiretroviral activity, modulation of the immune system, activity against opportunistic infections, or specific symptomatic relief.

Clinical effects that indicate the efficacy of a traditional medicine include the following:

(a) Decrease of symptoms such as diarrhoea, fever and pruritus, or improvement in appetite. Anecdotal reports of decreases in such symptoms should be interpreted with caution, however, as spontaneous remissions and exacerbations are apt to occur in the course of HIV infection. Greater certainty may be attached to such evidence, however, if symptoms go into remission for specific periods of time (e.g., fever or diarrhoea for at least one month) (see Annex 3).

(b) Disappearance of skin rash, Kaposi's skin lesions, lymph-node regression or increase in weight.

(c) Clearing of opportunistic infections such as candidiasis, cryptosporidiosis, herpes simplex, cryptococcosis or toxoplasmosis.

(d) Improvement in stage of disease (proposed WHO staging system, Annex 3).

Laboratory indicators may also be used, although the value of these measures is less than that of clinical end-points. Some laboratory measure that have been used include p24 core antigen, beta-2 microglobulin, serum/urine neopterin, CD4+ lymphocytes, total lymphocytes or erythrocyte sedimentation rate (ESR).

A variety of *in vitro* assays are available for assessing anti-HIV activity. *In vitro* assays for antiviral activity should be performed in accordance with the procedures described in the report on *in vitro*

screening for anti-HIV activity[1] with special emphasis on cellular tests that monitor the complete viral replication cycle.

2.2 Botanical species identification

Plant species selected for trial must be identified by the currently accepted Latin binominal and synonyms, with associated authority, if known, along with the common names by which the plant is known. The part(s) of the plant used to make the preparation should be indicated, as well as detailed instructions for harvesting (e.g., stage of growth), storage and processing prior to and following formulation. The appropriate parts of the plant, in a state of sufficient integrity to allow for physical identification, should be provided to a qualified botanist.

2.3 Thorough literature search and analysis of findings

In order to be able to predict secondary pharmacological effects and potential toxicities of plants selected for clinical evaluation in HIV-infected subjects, or those with AIDS, the scientific literature must be thoroughly searched for the following types of information:

(a) biological effects of extracts of the plant(s) in the preparation being considered for human studies (including plants in closely related taxonomic groups);

(b) occurrence of secondary metabolites in the plants and their biological effects. Analogues of these substances should also be considered.

Adverse effects of some plant secondary metabolites may not be demonstrated in acute toxicological studies, but may be predicted to occur after long-term administration. For example, most pyrrolizidine alkaloids will cause liver toxicity, which can be life-threatening after prolonged administration. Risk-benefit ratios must be assessed and a decision made about using plants for clinical studies that have anti-HIV activity but also contain such known toxic substances as pyrrolizidine alkaloids.

The team involved in an anti-AIDS drug study can carry out literature searches and make its own reports if adequate library facilities are available, including access to on-line computer systems such as MEDLINE, TOXLINE, BIOSIS and NAPRALERT.

By special arrangement with WHO's Traditional Medicine Programme, the WHO Collaborating Centre for Traditional Medicine, Chicago, will assist scientists, institutions and governments in developing countries by providing free access to the above-mentioned types of information from its NAPRALERT system.

Developing countries often have published information about local plants that is not abstracted or is unavailable in many developed countries; such information should not be neglected in the decision-making process. Established data banks are always pleased to receive such information.

2.4 Satisfaction of safety requirements

Pretrial toxicology requirements for all drugs are based on the proposed use of the drug and the information available regarding the interactions of the drug with biological systems. Traditional medicine products usually have a long history of use in humans. If acute side effects were severe and apparent, the use of the preparations would have been discontinued by traditional health practitioners. This hypothesis has been referred to as the "doctrine of reasonable assurance". Thus, acute toxicological testing in animals may not be indicated. However, toxicological tests should still be performed to ensure that any previously unobserved long-term toxic effects are detected in animal models prior to the development of the protocol for a clinical trial.

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[1] **Bulletin of the World Health Organization**, **67**(6): 613-618 (1989).

When experience with a herbal medicine is too limited to make an assessment of long-term toxicity with confidence, additional toxicological testing should be undertaken before a clinical trial is initiated.

The primary purpose of the testing is to identify potential target organs and to include appropriate monitoring of the system subject to insult. However, in patients with HIV infection and disease, the presence of a variety of secondary disease states/opportunistic diseases may severely weaken organ systems, unmasking new organ susceptibilities. Animal testing may therefore be of limited value in predicting toxicity in HIV-infected persons.

The nature of the disease state being treated is also a prime consideration in determining toxicological testing requirements. HIV infection gradually produces a terminal disease for which there is thus far no effective treatment. Every effort must therefore be made to test potential drugs promptly. A related consideration is that a traditional remedy intended for use in patients with advanced HIV disease may not require testing for long-term toxicity, since lengthy exposure to the drug will occur only in patients who are helped enough by it to sustain such an exposure. Chronic toxicity testing of such remedies may therefore be of dubious value. Extensive testing for long-term toxicity might better be reserved for herbal remedies that are considered for use in subjects in the relatively early stages of infection.

Toxicological tests in animal models should generally consist of a 90-day period of dosing by the route of administration intended for the clinical trial. Animals should then be necropsied and all major organ systems examined grossly and histopathologically. Such tests should be performed in two species, one of which is not a rodent. However, when adequate pharmacological or human experience exists, and national drug development policies do not require it, animal testing may not be necessary.

2.5 Adequate supply of the same plant material for all phases of the study

It is recognized that secondary plant constituents (including active principles) can vary both qualitatively and quantitatively in different lots of plant material. Therefore, it is essential that prelinicical testing and clinical studies be carried out on the same batch of plant material, collected at the same time from plants in the same general location. Enough material must be collected at one time, bearing in mind that, after appropriate drying, fresh plant material can lose up to 90% of its weight.

An appropriate voucher specimen representing the collection must be prepared and identified by a qualified botanist and stored for future reference. Air-dried plant material must be milled to a coarse powder and stored in air-tight containers to prevent contamination.

After a dosage form has been selected (decoction, infusion, etc.), the extract to be used in the studies should be freshly prepared daily by a qualified pharmacist and should be properly labelled with instructions for use. In studies that may involve a placebo-treated group, some work may be required to create a dosage form that has similar organoleptic properties using a plant known to be devoid of *in vitro* anti-HIV activity.

3. PLANNING A CLINICAL TRIAL

Careful consideration must be given to the planning of clinical trials. The trial protocol must be written and approved in advance, in consultation with experts representing various disciplines. The following experts should be part of the team or available for consultation:

(a) **Study coordinator** - to ensure the feasibility of the study plan, i.e., that all patients can be followed up and that records on each patient can be completed according to the protocol; and to be responsible for the conduct of the clinical trial.

(b) **Health care worker** (physician) - to evaluate background evidence to determine whether a clinical trial is justified to assist in defining the study population and the clinical end-points that signify therapeutic success; and to help in the design of patient questionnaires.

(c) **Nurse** - to develop a plan for routine health care associated with the trial; and to assist the health care worker in designing the study and determining the feasibility of the protocol requirements, taking into consideration existing health care capabilities.

(d) **Clinical pharmacologist** - to evaluate background information including safety data to determine whether a clinical trial is justified; and to assist in preparing the study design.

(e) **Pharmacist** - to verify the formulation of plant substances; to prepare material for administration to the control group; and to distribute test and control drugs to appropriate patients in accordance with study protocol.

(f) **Statistician** - to estimate the size of study population needed in order to achieve statistically significant results; to plan for the analysis of study results at the same time the study is being designed; and to assist in the design of forms for collecting data and patient questionnaires.

(g) **Traditional health practitioners** - to assist in the preparation of the test drug in collaboration with the pharmacist.

(h) **Social worker** - to develop a plan for counselling patients during the study; and to assist in ensuring that social and behavioural considerations receive attention in the protocol.

(i) **Others** - additionally, access to a botanist and a natural products chemist on an **ad hoc** basis should be secured for the duration of the trial.

The trial protocol should define the objectives of the trial and give full details of the selection and allocation of subjects, treatment and treatment end-points, criteria for withdrawal from and termination of the trial, follow-up procedures, and data recording and analysis.

3.1 Objectives

A simple, logical schema of the study objectives should serve as the introduction to the protocol.

3.2 Study sample

The sample population to be studied should be carefully defined.

The characteristics of subjects who qualify for the study should be summarized and include such information as age limits, sex, disease characteristics (e.g., severity, duration), and personal and social criteria that will ensure adequate participation in the trial (e.g., access to follow-up, ability to take medicine).

A similar list should be made of characteristics that disqualify a subject for the study, including other diseases and traits that may impair adequate participation in the study. Ordinarily, children and pregnant or lactating women are excluded from initial clinical trials.

The procedures to be used in recruiting subjects to the study should be outlined.

3.3 Allocation of subjects

Allocation of subjects to the various treatments included in the trial protocol should be made with due consideration to the following principles:

(a) **Informed consent**. Informed consent must be obtained from all study subjects according to all applicable standards of human rights and any relevant national regulations. Thus each subject must be given an adequate explanation of risk, benefit, and alternative treatments, and must be informed of his or her right to refuse to participate in the trial and, once in the trial, to withdraw from participation at any time.

(b) **Randomization**. Allocation should be randomized to avoid selection bias in the assignment of patients to treatment and control groups.

(c) **Stratification**, so as to achieve comparable control and treatment groups for purpose of analysis.

(d) **Control group**. An appropriate control group must be included as a basis for comparison with the treated group. Ordinarily, data on the control group are collected concurrently. Historical controls may be justified when the clinical course of any disease present in the treatment subjects is known to reach rapidly a clinically defined end-point. If there is no clearly beneficial treatment available, administering a placebo to the control group may be justified. Otherwise, the control group should receive the best alternative treatment available.

3.4 Treatment

There are many social and behavioural aspects of HIV infection and AIDS which must be addressed when conducting a clinical trial. The trial treatment plan must be considered in the context of the environment in which the patient lives and is treated.

The dose of the drug and its schedule of administration must be chosen. These may be based on the customary dosage for other uses. However, dose titration may have to be conducted early in the investigation in a group of patients to establish a tolerated dose range. This is often referred to as a phase I study. Effectiveness is then evaluated using this dosage range in what is termed a phase II study.

To limit any potential toxicity from the drug, procedures must be developed to monitor signs and symptoms that may indicate toxicity. Certain forms of toxicity may be suspected from prior experience, but both clinical and laboratory evidence must be monitored throughout the trial to detect events indicative of unanticipated drug toxicity.

A course of action must be planned for dealing with toxicity if it occurs. In some cases, it may be sufficient simply to lower the dose and allow the patient to remain in the study. In other cases the patient's participation in the study protocol may have to be discontinued.

3.5 Treatment end-points

Criteria for evaluating treatment must be standardized in advance. In the case of HIV infection and disease, however, the evaluation of any therapy is complicated by the large number of morbid events to which such patients are subject. A WHO staging system for HIV infection and disease has been proposed (see Annex 3)[1] and because end-points other than death are difficult to define, it is suggested that measures such as a comparison of the percentage of patients who remain in their starting stage in both treatment and control groups during the course of the trial might be used. Additional information will be gained by enumerating all the morbid events listed in the staging classification that occur in the treatment and control groups.

The sequence in the development of HIV-related clinical end-points and the time interval between them provides a clinical staging system which may be applicable only in a qualitative sense to patients in different communities. Thus such a general system may have to be modified to provide a specific instrument for the quantitative evaluation of individual clinical trials. The different spontaneous evolutions of the disease in different settings makes it essential that concurrent control groups are drawn from the same population in any therapeutic trial.

The stage of the disease should be assessed regularly and the trial continued long enough to determine whether the treatment has had any effect on the course of the disease. Because some of the evaluation parameters are subjective, bias may occur in the evaluation of patients. It may be crucial, therefore, to design the trial so that both patients and those gathering study outcomes are unaware of whether the patient has taken the study drug or is in the control group. Sometimes, however, this double-blind study design is not feasible. Under these circumstances a single-blind design may be used, in which either the patient or the health worker is unaware of whether the patient has been assigned to the treatment or the control group.

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[1] **Weekly epidemiological record**, **65**, 221-228 (1990).

3.6 Criteria for withdrawing a patient from the trial

Criteria for withdrawing a patient from the trial, such as failure to adhere to the trial protocol, must be adopted before the trial begins.

3.7 Criteria for terminating the trial

Criteria for terminating the trial must also be adopted in advance. Two such criteria are: (a) unacceptable toxicity of the drug; (b) evidence of success or failure of therapy.

3.8 Follow-up

A schedule must be adopted to determine what information will be obtained at each follow-up visit. Such information should include a check-list of clinical symptoms (reported by the patient), clinical signs (reported by the health worker), and laboratory values. The optimal amount of information to be collected in a clinical trial may be difficult to determine. Gathering more information than absolutely necessary makes the trial cumbersome and may jeopardize its success. On the other hand, the systematic collection of data within the framework of a clinical trial may yield unanticipated data that prove valuable for further studies.

3.9 Data recording

An accurate record should be maintained for each patient during the trial. This record should describe the characteristics of each patient entering the trial, as well as the subsequent clinical course. Records of this kind facilitate the assembly of the basic data needed for any therapeutic trial. The record forms must be designed so as to provide space to enter all required data concisely to facilitate the complete, accurate and efficient collection of all necessary data. It is recommended that the following records be maintained for each patient:

(1) Enrolment record

(a) Has informed consent been obtained and documented?

(b) Basic patient information, e.g., date of birth, sex, and race.

(c) Check-list related to the present illness, which includes duration and a brief description of each relevant symptom.

(d) Check-list of required diagnostic tests.

(e) Treatment schedule.

(f) Check-list of other drugs taken.

(g) Check-list for exclusion criteria, e.g., childhood, pregnancy, lactation, and drug allergy.

(2) Medical history and physical examination record

(a) Review of symptoms, which might include a check-list as well as space for a brief description of any positive findings.

(b) Physical examination, which includes weight, a list of vital signs, and a check-list indicating which systems are normal and which are abnormal.

(3) Follow-up evaluation record

(a) Date of visit - visit number.

(b) Interim historical information.

(c) Medication compliance evaluation.

(d) A recording of adverse events, including a check-list of those anticipated, as well as other events that may indicate serious unanticipated toxicity.

(e) A list of any concurrent drug therapy, including self-medication.

(f) Clinical evaluation, which includes height, weight, vital signs, and specific signs and symptoms of the disease.

(4) Laboratory results

Laboratory results should be recorded on a form that lists the date together with values for such data as haematology, blood chemistry, and urine analysis that are required for the trial.

Record keeping

Individual records must be checked to ensure that they are complete. Then data from individual records must be compiled for analysis.

3.10 Data analysis

Statistical aspects of the trial must be considered in advance. An estimate must be made of the number of patients needed in the study to make it likely that a statistically significant result will be attained if the treatment is as effective as anticipated. Ordinarily, a plan for data analysis should be determined in advance, along with any necessary rules for stopping the trial, if the anticipated results of the trial are obtained earlier than expected.

Analysis of trial results may be carried out on an interim basis to assure that no unanticipated toxic events are occurring and to ensure that the trial is not continuing beyond the point needed to achieve the study objectives. Sometimes it may be necessary to have an independent committee to monitor interim results. However, when all results have been obtained, the analysis should be carried out in the manner that was specified when the trial was designed. In addition, however, a great deal may be learned by examining the data to determine whether they suggest unanticipated results that may have therapeutic or scientific interest or that may suggest hypotheses for future studies.

Analysis must also be made of data on all patients who have left the trial, including their fate and the reasons they left the trial. An effort must be made to trace every such patient.

ANNEX 3

PROPOSED WHO CLINICAL STAGING SYSTEM FOR HIV INFECTION AND DISEASE[1]

The WHO Global Programme on AIDS has issued the following proposed clinical staging system for HIV infection and disease. Based primarily on clinical criteria, the system is organized into four prognostic categories. It also incorporates a performance scale based on the Eastern Cooperative Oncology Group score.

Clinical stage 1:

1. Asymptomatic.

2. Persistent generalized lymphadenopathy (PGL).

   Performance scale 1: asymptomatic, normal activity.

Clinical stage 2:

3. Weight loss of < 10% of body weight.

4. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis).

5. Herpes zoster, within the last 5 years.

6. Recurrent upper respiratory tract infection (i.e., bacterial sinusitis).

   And/or Performance scale 2: symptomatic, normal activity.

Clinical stage 3:

7. Weight loss of > 10% of body weight.

8. Unexplained chronic diarrhoea, > 1 month.

9. Unexplained prolonged fever (intermittent or constant), > 1 month.

10. Oral candidiasis (thrush).

11. Oral hairy leukoplakia.

12. Pulmonary tuberculosis, within the past year.

13. Severe bacterial infections (i.e., pneumonia, pyomyositis).

    And/or Performance scale 3: bed-ridden < 50% of the day during the last month.

Clinical stage 4:

14. HIV wasting syndrome, as defined by the Centers for Disease Control (CDC).[2]

15. *Pneumocystis carinii* pneumonia.

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[1] **Weekly epidemiological record, 65**: 221-228 (1990).

[2] HIV wasting syndrome: Weight loss of > 10% of body weight, plus either unexplained chronic diarrhoea (> 1 month), or chronic weakness and unexplained prolonged fever (> 1 month).

16. Toxoplasmosis of the brain.

17. Cryptosporidiosis with diarrhoea, >1 month.

18. Cryptococcosis, extrapulmonary.

19. Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes.

20. Herpes simplex virus (HSV) infection, mucocutaneous (>1 month) or visceral (any duration).

21. Progressive multifocal leukoencephalopathy (PML).

22. Any disseminated endemic mycosis (i.e., histoplasmosis, coccidioidomycosis).

23. Candidiasis of the oesophagus, trachea, bronchi, or lungs.

24. Atypical mycobacteriosis, disseminated.

25. Non-typhoid **Salmonella** septicaemia.

26. Extrapulmonary tuberculosis.

27. Lymphoma.

28. Kaposi sarcoma (KS).

29. HIV encephalopathy, as defined by CDC.[1]

    And/or Performance scale 4: bedridden >50% of the day during the last month.

(Note: Both definitive and presumptive diagnoses are acceptable.)

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[1] HIV encephalopathy: Clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.