Report of the of the International Conference on

TRADITIONAL MEDICINE IN
HIV/AIDS AND MALARIA

December 5-7, 2000
Nicon Hilton Hotel
Abuja, Nigeria

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"Recall the face of the poorest and the weakest man whom you have seen, and ask yourself, if the steps you contemplate are going to be any use to him. Will he gain anything by it? Will it restore to him control over his own life and destiny?" Mahatma Ghandi

EXECUTIVE SUMMARY

Many research institutions and independent investigators in Africa have reported positive clinical outcomes in the use of traditional medical remedies for the treatment of HIV/AIDS and malaria. The results of these investigations, however, have not contributed in any significant manner to either the drug development efforts or treatment of these diseases. This is due to lack of technical support in the design and execution of these studies, especially in having access to validated protocols, the biochemical analysis and standardization of the herbal remedies and phytomedicines. It is against this background that the International Conference on Traditional Medicine in HIV/AIDS and Malaria was held on December 5 through 7, 2000 at the Nicon Hilton Hotel in Abuja, Nigeria. The conference was delimited into five broad themes dealing with Policy Issues, Regulations and General Overview, Recent Advances in Traditional Intervention Systems for HIV/AIDS, Advances in Traditional Medicines for Malaria, Standardization and Evaluation of Traditional Medicines, Protocols for Clinical Research Creating, and Enhancing and Maintaining Collaborative Research. The conference also hosted a Special Forum for Traditional Medical Practitioners as well as a poster session that displayed papers on HIV/AIDS and malaria from all over the world. Four thematic working groups were created and they met at different times during the conference to discuss the issues and the possible outcomes surrounding their respective themes of Malaria, HIV/AIDS, Policy and Intellectual Property Rights and Standardization. During the plenary session on the reports of the thematic working groups, a Communiqué was developed simultaneously which was then discussed and agreed upon by the conference participants as a formal declaration.

Approximately 100 participants attended the conference sessions. This includes scientists, policy makers, traditional healers, orthodox practitioners, anthropologists, pharmacologists, toxicologists, medicinal chemists, biologists and naturopathic physicians. Conference attendees came from all over the world including various locations in Nigeria, Cameroon, Senegal, Kenya, Ethiopia, Uganda, Zambia, South Africa, Jamaica, Germany, England, Portugal, Sao Tome and Principe, Switzerland and the United States.

In conclusion, the conference provided a multi-sectoral platform for a thorough review of the use of traditional medical system in the treatment of HIV/ AIDS and malaria. In the process, it has established a network as well as strategies for a continuum between research projects in traditional medicine in HIV/AIDS and malaria, and translation of this type of indigenous research and development efforts into useful clinical tools. The conference also took into consideration the various national strategic plans and it created a working partnership between governmental agencies, academic institutions, training institutions, community leaders, scientists and policy makers who are stakeholders in the global fight against HIV/AIDS and malaria. It provided information to the participants on the current status of leading herbal medicinal products under various stages of development as potential agents for the treatment of HIV/ AIDS and malaria.

Accordingly, the need has arisen for the development of an institutional framework for technical assistance on the biochemical analysis, standardization, safety assessment and clinical outcome studies of herbal medicines to traditional healers, institutions and scientists involved in the development of traditional medicine for HIV/AIDS and malaria. In addition, there is also a need for assistance in the use of legal instruments to protect the Intellectual Property Rights of traditional healers and African institutions involved in the development of herbal medicines and phytomedicine from traditional knowledge. This includes the use of a trust fund mechanism for both benefit

sharing and the intermediation of credits to micro enterprises as demonstrated by the Fund for Integrated Rural Development and Traditional Medicine. The conference requested that InterCEDD should institute as a matter of urgency a training programme to address these two areas of need and to seek funds to establish a technical assistance project for institutions in Africa working on the development of herbal medicinal products (not as sources of chemical compounds but as therapeutic agents) for the treatment of HIV / AIDS and Malaria.

Conference Objectives

- Review the results of traditional intervention systems available for the treatment of HIV/AIDS and Malaria.

- Identify promising traditional remedies in current use for the treatment or management of these diseases.

- Provide guidelines for the biochemical evaluation and standardization of traditional medicinal products and herbal remedies used in the treatment of HIV/AIDS and Malaria.

- Develop and harmonize methods and protocols available for clinical outcome evaluation safety and efficacy of traditional medical treatment of these diseases.

- Establish a forum for the exchange of ideas for research and treatment of these diseases.

PLENARY SESSIONS

OPENING REMARKS

Prof. Elijah Sokomba, BDCP, Lagos, Nigeria, began the first presentation at the conference by welcoming all participants to the meeting, noting that their participation in the conference was an eloquent effort to show their dedication to traditional medicine. Prof. Sokomba then provided background on the conference organizers and collaborators, InterCEDD, BDCP, Association for the Promotion of Traditional Medicine (PROMETRA), National Institute for Pharmaceutical research and Development (NIPRD) and African Scientific Co-operation on Phytomedicine and Aromatic Plants (ASCOPAP) as well as the sponsors, the Ford Foundation, New York and Lagos and the Multilateral Initiative on Malaria (MIM), NIH and the conference supporters including, Tropical Disease Research, World Health Organization (WHO), the International Cooperative Biodiversity Group, Africa, the Bioresources Development and Conservation Programme and the Columbus AIDS Task Force, Ohio. He then placed the meeting into perspective by reminding participants that the lack of appropriate policy framework has greatly impeded the evaluation and utilization of traditional medicines in AIDS and malaria control, and there is a need for full disclosure of knowledge. Prof. Sokomba then noted that the ultimate goal of this conference was to strengthen the capacity of traditional healers to develop treatments for HIV/AIDS and malaria.

The official opening was made by Dr. Tolu Fakeye, of the Federal Ministry of Health on behalf of the Nigerian Minister of Health, Dr. Tim Menakaya. Dr. Fakeye expressed his excitement to address such a distinguished gathering of scholars, traditional medicine practitioners, scientists and policy makers assembled for the purpose of advancing the control of two very important disease entities, HIV/AIDS and malaria. He then continued, stating that HIV/AIDS and malaria are together responsible for the bulk of the morbidity and mortality underlying the poor health profile of Nigerians. The pertinent question to pose at this workshop therefore is, how can traditional medicine contribute appreciably to the control of these disease entities? He remarked that we must continue to develop strategies that will ensure that traditional medicine can be involved at all levels. To date not many traditional remedies have been certified or registered in Nigeria, and as a result we need to facilitate the process of product development and establish traditional medicine institutions. In closing, Dr. Fakeye, expressed confidence in the participants collective capabilities to deliberate productively on the conference objectives in order to offer sound recommendations for the successful utilization of traditional medicine to facilitate the control of HIV/AIDS and malaria in Nigeria.

Prof. Maurice M. Iwu - InterCEDD/BDCP, in presenting the conference overview explained that the underlying problems are the economical circumstances of Third World countries, which create depressing health situations in most developing countries. He then continued by stating that there are no approved drugs to date that has been developed based on the excellent hard work done by investigators on traditional medicines and this in itself is an incentive to review of our strategies and methodology in order to better serve the health-care needs of patients in developing countries suffering from AIDS and malaria. We need to look at the high percentages of HIV/AIDS and the lack of access to modern therapies as an added incentive. Another big issue is multi-drug resistance with malaria. We have to come up with ways to overcome these problems. Prof. Iwu then asked the question of, if there are new drugs being developed in the USA and Europe why do we not see

developments in Africa or Latin America and Asia where these diseases are endemic? There is a significant amount of information and skill available in sub-Saharan Africa, but it is not accessible to those who need it most. He emphasized this point by stating that in our experiences with product development here in Nigeria and South Africa the raw materials are often identified here and developed in the USA or Europe. Thus why is it not possible to act out the entire process here in Africa?

He proceeded to outline the main themes of the conference and explained he expected positive outcomes from the meeting. In its continuing efforts to come up with practical solutions surrounding the utilization of traditional medicine for the treatments of HIV/AIDS and malaria, the conference organizing committee focused the plenary sessions on policy issues and regulations, recent advances in traditional intervention systems for HIV/AIDS and malaria, standardization and evaluation of traditional medicines, and creating, enhancing and maintaining collaboration. Throughout the three-day conference, various plenary session presentations focusing on these issues were given by scientists, practitioners, traditional healers and policy makers. The presentations were designed to provide insight into the issues raised and concerns expressed about the relationship and role of traditional medicine in the fight against HIV/AIDS and malaria. He introduced the contents of the working papers and reference papers included with the conference materials.

The plenary session presentations included:

Track A: Policy Issues, Regulations and Overview: The lack of appropriate policy framework has greatly impeded the evaluation and utilization of traditional medicines in AIDS and malaria control. It has also prevented progressive strengthening of national and local capacities for assessing clinical situations and selecting appropriate measures aimed at reducing or preventing these diseases. A significant part of the traditional interventions involve the use of knowledge collected from indigenous native populations and therefore serious thought must be given to resolving inherent ethical, social values and policy issues. This session reviewed how and to what extent cultural, ethical and social structures can be incorporated into technical and scientific drug development. Discussions and debates on intellectual property systems, patent requirements and international agreements were also included.

Track B: Recent Advances in Traditional Medicine Systems for HIV/AIDS: Of the 16.3 million AIDS-related deaths reported through 1999, 13.7 million occurred in Africa. Each day, about 5,500 African men, women and children are buried as a result of the AIDS virus. Reports have shown that by the end of this year, 10.4 million African children under the age of 15 would have lost one or both parents to AIDS. Many research institutions and independent investigators in Africa have reported positive clinical outcomes in the use of traditional medical remedies in the management of AIDS. These results however have not contributed in any significant manner in drug development efforts. Case studies and advances in the treatment of this disease were discussed.

Track C: Recent Advances in Traditional Medicines for Malaria: Malaria is by far the world's most significant tropical parasitic diseases, and kills more people then any other communicable disease. Worldwide prevalence of the disease is estimated to be in the order of 300-500 million clinical cases each year. More than 90% of all malaria cases are in sub-Saharan Africa. Recent research, traditional remedies and interventions in the management of drug-resistance malaria were reviewed.

Track D: Standardization and Evaluation of Traditional Medicines: Development of phytomedicines could provide a more affordable, and in some cases more effective, form of local health care. This session addressed criteria for evaluating the quality, safety and efficacy of herbal medicines. Guidelines for the biochemical evaluation as well as national and international policies on regulation of phytomedicines were discussed.

Track E: Protocols for Clinical Research: A translation of indigenous research and development efforts into useful tools will significantly boost the available tools for the treatment of AIDS and malaria. This would also mean substantial improvement in medical surveillance, biomedical literature and clinical based research on these diseases. The conference aimed to develop and harmonize methods/protocols available for clinical outcome evaluation of the safety and efficacy of these traditional medical interventions.

Track F: Creating, Enhancing and Maintaining Collaborative Research: HIV/AIDS and malaria undermine education, agriculture, and business in Africa while at the same time, taxing already overstretched health services. Poverty is getting worse just as the need for more resources to curb the spread of these diseases and alleviate the epidemics' impact on development is growing. There is therefore an urgent need for meaningful sustainable collaboration among scientists, traditional healers, policy makers, local communities and international organizations. This session discussed funding opportunities, on-going collaborations and resources available locally and internationally.

PRESENTATIONS MADE DURING THE SPECIAL FORUM FOR TRADITIONAL MEDICAL PRACTITIONERS

The Special Forum for Traditional Medical Practitioners provided three distinguished traditional medical practitioners with a space to share with conference participants the important and successful work they are carrying out in their respective countries. As it was said many times throughout the conference, "we are in this together, and we must help and learn from one another," this forum was an ideal time for traditional healers, orthodox practitioners, scientists and policy makers to listen and learn from one another. The following is a summary of the speaker's key points:

- Mercy Manci, of South Africa opened the special forum by talking about various strategies traditional healers use in South Africa when they are providing care to HIV and malaria patients. Mrs. Manci explained the "mountain of life," and the "tree of life" strategies they use to help their patients and patient's families understand their illness, the prevention of the illness and habits and treatments that the patients can use to return to a healthy stage.

- Ohyu Azidjah, one of Nigeria's foremost healers began by explaining a little bit about some of the treatments she uses for malaria, typhoid and HIV/AIDS. She then proceeded to explain that traditional healers can tell you the name of the leaves and the dosage, but the problem is that they can never tell you exactly. Traditional healers cannot tell you precisely because they are afraid that they will lose the knowledge to you. She further noted that traditional healers will become lecturers and they will be paid just like everyone else in the university when this environment no longer allows people to carry knowledge away and use it in a different spirit.

- Erik Gbodossou, President of the Association for the Promotion of Traditional Medicine, Senegal, gave an overview of the self-proficiency method they use at his clinic. This method is a way to help traditional healers help more of the population. Dr. Gbodossou explained how first they create a scientific committee that performs a KAP study and then a qualitative survey of the traditional healers knowledge on a certain theme. With this knowledge they form a large database of all of the traditional healers knowledge that they then use to train the traditional healers. He then stressed their goal of giving the traditional healers their own knowledge to help them claim this knowledge and become better IEC agents (Information, Education, Communication).

SYNOPSIS OF INTERCEDD/BDCP REVIEW OF HERBAL ANTIMALARIAL AGENTS

1. InterCEDD/ BDCP Antimalarial Programme

The presentation provided an assessment of malaria drug resistance worldwide and insight on the status of various candidates from traditional medicine that may be potential therapeutic agents for the treatment of drug resistant malaria. Most of the clinically available drugs, the report noted, have serious problems that limit their usefulness as drugs of choice for the treatment of multi-drug resistant malaria. Some of the new drugs such as Halofantrine and Mefloquine are considered too toxic by some clinicians that they have not been well accepted as good therapeutic agents. The increases in the incidences of malaria due to drug-resistant parasites and the need for more effective and safer drugs have necessitated the search for new malaria agents. InterCEDD in collaboration with the ICBG programme and several institutions in U.S.A., Europe and Africa has an ongoing project for the identification and evaluation of new drugs for treatment of drug resistant malaria and for prevention of malaria worldwide. As a follow-up to this conference, InterCEDD and BDCP hope to select phytomedicines and related natural products molecules for transition to advanced development as low-cost medicines to treat multi-drug-resistant malaria. The project will also provide technical assistance or initiate a project to select candidate molecules for transition to advanced development as drugs to treat severe and complicated malaria. The project will continue its project to identify herbal medicinal products for transition to advanced development to prevent multi-drug-resistant malaria and new classes of compounds that focus on combination of antiplasmodial effect with immune stimulatory activity.

2. Natural Product Compounds and Related Molecules

The introduction of the sesquiterpene lactone, artemisinin from the Chinese herb *Artemisia annua* and the hydroxynaphtoquinone, atovaquone as new chemotypes for the treatment of malaria have raised the hope for the discovery of even better antimalarial agents. Although the natural product origin of the atovaquone molecule may not be very obvious, the similarity in the structure of the compound to the naturally occurring hydroxylapachol is very interesting. It increases the need to re-examine the many naphtoquinones associated with the antimalarial activity of several medicinal plants for further development. A major effort has been in the preparation of several semi synthetic derivatives of artemisinin aimed at developing new class of antimalarials with improved pharmacokinetics. It appears that the unique endoperoxide moiety in artemisinin has been retained in most of the derivatives being tested, which raises the possibility that the neurotoxicity encountered with the parent molecule may still be present in the new molecules.

A review of the documented literature on compounds tested for activity against *Plasmodum falciparum* shows that certain chemical classes hold greater promise for the development of new antimalarial agents. Promising chemotypes for development include, bisbenzylisoquinolines protoberberines, indole alkaloids, quassinoids, naphtoquinones, quinolines, naphthylisoquinolines and indoloquinolines. It is important that on-going work in these classes of compounds should be completed as most cases of the introduction of new compounds involved use of cumulative knowledge of a given molecule discovered many years before their eventually acceptance as drug molecules. The artemisinin story is a good example to illustrate this point[1]. The use of the plant for

[1] Ziffer, H., Highet, R.J. and Klayman, D.L. (1997) "Artemisinin: An Endoperoxidic Antimalarial from *Artemisia annua* L" In: Herz, W. *et al*. eds. . Progress in the Chemistry of Organic Natural Products, **72**: 121-214.

the treatment of malaria was 'discovered' in the 1960's by Chinese scientists and the structure of the pure compound was published in 1971 but it was not only until 1984/85 after the publication of the monumental paper by the late Daniel Klayman that the full potential of the new agent was widely acknowledged. It took several more years before a clinically acceptable drug was available. Another example is presented by the naphthoquinoids, which were recognized as early as the 1940s to be responsible for the antimalarial activity of many medicinal plants used in traditional medicine. Many synthetic naphathoquinoids were tested for their antimalarial activity, including lapinone (a 1,4-hydroxynaphoquinone, HNQ) and menactone in a search for compound with better antimalarial properties than naturally occurring hydroxylapachol. Some of the analogues reached clinical trials but further development of HNQs culminated in atovaquone, which in combination with proguanil has been introduced recently for the treatment of *P. falciparum* malaria[2]. Our group has examined the relationship between the *in vitro* antiplasmodic activity of several plant antimalarial extracts and the cytotoxicity effects in cell lines. We were able to establish that a correlation does exist between the two activities but the antimalarial activity of the extracts occur at concentrations that will not make the extracts suitable candidates for anticancer drug development.

3. Herbal Medicinal Products

Several herbs used in traditional medicine have been validated by scientific evidence for their efficacy and safety[3]. Attempts to isolate the active constituents and develop them into therapeutic agents have posed far more challenges than was anticipated. The usual sequence in drug discovery based on traditional medicine is the identification of the herbs used by traditional healers and subjecting them to *in vitro* bioassay. This has not been as successful as would be expected given the resources and time expended in bioassay guided separation of plant extracts. Due to reasons which are not completely well understood, some plant extracts appear to have biological activity that are superior to that of the isolated pure compounds. The organic fraction of the alcoholic extracts of *Enantia chlorantha* and *Ancistrocladus* spp. for example, showed greater antiplasmodial activity than the individual compounds isolated from them. In other cases, the *in vivo* laboratory results did not correlate with either the ethnomedical evidence or the clinical observations. The *in vivo* antiplasmodial activity of, *Pothomorphe umbellata*, a well known traditional Brazilian antimalarial plant could not be confirmed using the standard intraperitoneal *Plasmodium berghei* mice model[4]. The activity of Crytoplepine, the active constituent of the West African antimalarial herb *Cryptolepis sanguinoleta* could not be confirmed for long-time due to the inability of several investigators to observe a positive *in vivo* result from *P. berghei* infected mice model treated intraperitoneally with the compound. These examples re-emphasize the need for the development of better *in vivo* models for the testing of antimalarial drugs. There are several examples indicating the synergistic effect of multiple constituents of individual herbs or a combination of herbs to achieve a therapeutic effect not observable with individual compounds. The development of traditional herbal medicine is further complicated by the almost usual addition of a volatile oil containing plant in the formulation. It was previously believed that these herbs apparently with little or no antiplasmodial activity serves as flavoring agents to mask the often bitter tastes of the herbs but recent evidence suggest that spices such as *Piper guineensis* not only enhances the absorption of certain drugs but play crucial roles in the overall pharmacokinetic profile of certain drugs. *Artemisia annua* extract used in Chinese

[2] Croft, S.L. and Weiss, C.R. (1999) "Natural Products With Antiprotozoal Activity" In: Bohlin L.and Bruhn, J.G. Eds. Bioassay Methods in Natural Product Research and Drug Development, Proceedings of the Phytochemical Society of Europe., Vol. 43: 81-99. Kluwer Academic Publishers, Dordrecht

[3] See Okunji, C.O. *et al*, in this report; Kirby, G.C. 1997, Tropical Doctor, Supplement 1: 7-11.

[4] De Ferreira-da-Cruz M., *et al*. 2000: *Exp. Parasitol.* **94**(4): 24 3-7.

ethnomedicine consists of aqueous decoction but the isolated active constituent, artemisinin is highly lipophilic and could not have been entirely responsible for the antimalarial activity observed with the water extract. It has been suggested that congeners such as the structurally unrelated flavonoids, also present in the plant enhance the antiplasmodial properties of the sesquiterpene lactones that are largely responsible for the antimalarial activity. Other species of Artemisia that do not contain artemisinin have also been found to possess antimalarial activity, which further suggests the presence of yet unidentified antimalarial constituents in these species..

Synergism between plant-derived compounds and standard antimalarial drugs such as chloroquine has been demonstrated in both laboratory and clinical studies. Examples include the bisbenzylisoquinoline alkaloids 7-O-demethyltetradrine isolated from *Strychmopsis thoruarsii* and limacine (7-O-demethylphaenthine from *Spirospermum penduliflor*u, Strychnous alkaloids strychnobraziline and malagashimine. Another interesting interaction between natural products and standard antimalarial agents is the observation that some of the bisbezylisoquinolines showed potential ability of reversing chloroquine resistance *in vitro*. There have also been some reports of apparent antagonism between standard antimalarial agents and herbal remedies. Most of the verifications of this problem have been from *in vitro* studies. Further observational studies are needed to confirm the existence of this problem.

4. Diet, Malaria Prevention and Immunotherapy

Several plants used as ingredients of normal diet in malaria endemic parts of the world, albeit as occasional food, have been shown by laboratory studies to possess significant antimalarial activity. The activity in some cases has been confirmed by *in vivo* animal studies. Many of them do not possess remarkable antiplasmodial activity *in vivo* when compared with standard drugs such as chloroquine or artemisinin but it is highly possible that the use of such herbs as dietary substances may act as immune stimulants or merely arrest or slow down the effect of the parasite. In effect, these agents are not necessarily antiplasmodic agents but prevent the development of malaria in the human body. Notable examples from our own work include *Vernonia amygdalina, Combretum micranthum, Annona senegalensis, Moringa oleifera, Vitex rivularis,* and the ingredients of various steam therapy, including guava, mango, lemon grass, and neem. This class of herbal medicinal products does not easily fit into the classical definition of medicinal agents and may require a different protocol for their proper evaluation..

It has also been observed that many traditional plant-derived remedies appear to be effectual only in indigenous users who have previously been exposed to malaria and hence has some degree of immunity. It is possible that some of the traditional remedies are able to reverse the pathological effects of the disease without necessarily completely eliminating the causative organism.[5] This raises a major issue in the selection of potential agents for development as antimalarial drug: that there is a major (and often overlooked) difference between the requirements for those used in western medicine, where malaria patients can be expected not to display immunity to the disease, and that of populations constantly exposed and having some degree of immunity. It is further agued that for western patients plasmodicidal drugs, which actually kill the parasite, are likely to be a priority, as against the need in exposed populations where the clinical preference may be for plasmodistatic compounds, immune stimulants and antipyretics that are able to arrest or even reverse the pathological consequences of the infection. It is noteworthy that both eradication of the parasites

[5] Kirby, G.C. (1996) Medicinal Plants and the Control of Parasites, Transactions of the Royal Society of Tropical Medicine and Hygiene. 90: 605-609.

and promotion of pathological effects of the disease are mediated through the immune system and it is quite possible that many of the traditional herbal remedies act by differential effect on both causation and pathogenesis of diseases whereas most drug discovery strategies are limited to new drugs that selective kill the parasites. Kirby (see footnotes for references) has persistently raised this problem as a major consideration in the antimalarial drug development debate and has even suggested the possibility of a conflict of interest from the point of view of developed world institutions in concentrating efforts in the development of antiplasmodic agents with 'global' application, which is a tacit acceptance that development of a drug targeted to the poor living in malaria endemic regions remains an unacceptable expenses, given the unlikely possibility that developing world will be able to repay the enormous investment required to develop drugs for tropical diseases.

SYNOPSIS OF INTERCEDD REVIEW OF PLANT ANTIVIRAL AGENTS AND HERBAL MEDICINAL PRODUCTS FOR OPPORTUNISTIC INFECTIONS IN HIV/ AIDS.

The conference had the opportunity of having as working papers two recently published references on the subject of this discussion. The two articles provided a summary of the inhibitors of HIV reverse transcriptase (rt)[6] and major compounds for general chemotherapy of HIV derived from plants[7]. The present review merely updates these two excellent reports and provides additional information on the status of some of the drug candidates covered in the earlier reviews and new materials not available at the time of the two publications. Given that this is a rapidly evolving research topic, we have also included discussions on compounds and extracts that have not been published, which are taken from the work from our group and submissions from others who are unable to make it to the meeting.

1. Inhibitors of HIV Reverse Transcriptase (RT)

The introduction of the potent RT-inhibitor 3'-azido-3-deoxythymidine (AZT) has had a remarkable impact in the management of human acquired immuno-deficiency syndrome (AIDS). The drug originally described in 1974 as being active against murine retroviruses was adopted for the human infection following the recognition of the association between AIDS and a retrovirus, HIV. The success of AZT and related compounds and the high cost of the drugs have given impetus for the search for better and more effective RTs. Many natural products have been shown to possess significant activity, at least *in vitro* studies, at concentrations that are comparable to the synthetic RTs. The compounds vary enormously in their chemical structures, they include alkaloids, flavonoids, lignans, coumarines, naphthoquinones, antraquinones, polysaccharides and terpenes,. The most important examples include the novel naphthoquinones michellamines A-C isolated from the rare tropical plant *Ancistrocladus korupensis* obtained from Cameroon, calanolide A, isolated from Calophyllum lanigerum, and putranjivain A from the Egyptian plant *Phyllanthus embelica*.

2. Other Antiviral and Immuno-Modulatory Agents

The exact mode of action of several plant-derived antiviral agents has not yet been determined but some of them have been shown to exhibit significant activity against HIV, a virus associated with AIDS. This category of antiviral agents was also considered important since they may provide additional insights into the possible biochemical mechanism of the treatment of AIDS. These compounds either interfere directly in various stages in the replication cycle of HIV or strengthen the patients' immune system against the devastating effect of the infection. The list includes substances that exhibit the following inhibitory activities against HIV: protease inhibition, virus adsorption, glycosylation, virus-cell fusion, assembly/ release, translation, integration, etc. Compounds in this group that have been studied under clinical setting include castonospermine, glycyrrhizin, papaverine, trichosanthin, aceramannan, and N-butyl-1-deoxynojirimicin. An issue that arises is that given the fact that most of these substances have far greater safety record than the much promoted nucleoside RT inhibitors and the several commercial cocktails based on their use in combination therapy, what is the mitigating factor that has prevented the wide-scale use of these plant-drugs. It may be necessary to re-examine the validity of our current objectives in the development of new anti-HIV drugs for traditional medicine. Should the target of our search be

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[6] Matthee, C., Wright A.D. and Konig, G.M. (1999) HIV Reverse Transcriptase Inhibitors of Natural Origin, *Planta Medica* **65**: 493-506

[7] Vlietinck, A.J. *et al*. (1998) *Planta Medica* **64**: 97-109

to discover novel drugs of global importance that are better and different than AZT or to seek therapeutically or pharmacodynamically equivalent medicine that may be a good substitute for imported synthetic drugs?

As was previously indicated in this report, some of the traditional remedies used in for the treatment of HIV/ AIDS do not necessarily fit into the classical antiviral chemotherapeutic agents. Given our inadequate understanding of the relationship between HIV replication and the pathogenesis of AIDS, the clinical benefits of these drugs can only be realized from information obtained from their proper use rather than the view held among some regulatory agencies that only U.S. FDA approved products with clearly documented efficacy and safety should be allowed in AIDS clinics. A large number of clinical studies have demonstrated the enormous benefits of highly active anti-retroviral therapy (HAART) in the management of HIV infections as evidenced by resolution of opportunistic infections and malignancies, as well as declining hospitalization and mortality rates. This suggests that potent and sustained suppression of viral replication, at least to some extent, is associated with reconstitution of the immune system even in adult patients treated at advanced stages of the disease. Combination of these natural HAARTs with immune system enhancers holds a lot of promise in the treatment of AIDS.

Our group has examined the usefulness of the combination of the highly specifically standardized mixture of Astralagatan (*Astralagus membraceous*), Tinosporin A (*Tinospora cordifolia*), glycyrrhizin (licorice, *Glycyrrhiza glabra*), Alloerein (Alloe babardensis) and Kolaviron (Garcinia kola), with multivitamin. The mixture like most plant extracts may be capable of non-specific stimulation of the immunological defense mechanisms. The evidence obtained so far can only be regarded as anecdotal until a controlled evaluation of the product has been conducted. It has been observed that such non-specific stimulants do not affect immunological memory cells and since their pharmacological efficacy fades comparatively quickly, they have to be administered either at intervals or continuously[8]. The product like similar dietary supplements may be used as an adjuvant with existing antiviral medication if so approved by the attending physician.

In a related study with *Kolaviron*, a mixture of C-3/ C-8"-linked biflavanones, GB1, GB2, kolaflavanone, and the rare benzophenones, kolanone, found in the seeds of the West African tree *Garcinia kola*, was found to possess dose dependent activity against certain viruses including HIV and Ebola virus. This food plant, used in African folk medicine as a general antidote, is an ingredient in commercial herbal formulations as an "immune tonic". Preliminary studies using Luminetics™ assay for T cell activation indicate that *kolaviron* and one of its major components GB-1 also show immune potentiating properties in whole blood cultures, from normal and HIV-infected patients, concomitant with the addition of mitogens or recall antigens. *Kolaviron* alone was not immunostimulatory and ATP responses were dose dependent. The compound showed no toxic effects on cells making it a potential candidate for development as a drug for the control of HIV replication and immune reconstitution. A follow-up study is planned, which will undertake the following: a) use preparatory scale HPLC to obtain large quantities of *kolaviron* and GB-1 for further biological testing against HIV replication and b) assay the compounds for T-Cell activation by measuring the immune function of various sets or subsets of T-lymphocytes by comparing the level of activation of stimulated cells with unstimulated cells. The studies will determine the effect of *kolaviron* on the general immune status in specimens from normal individuals and those with certain

[8] Wagner, H. (1990) "Search for plant derived natural compounds with immunostimulatory activity", *Pure & Appl. Chem*. **62**: 1217-1222.

immunodeficiencies as occurs in AIDS patients. It will also seek to determine the differential activities of various constituents of *kolaviron* in these assays. The eventual application of this work is to develop a drug for use in immune-reconstitution in individuals with immunodeficiencies as occurs in AIDS patients or patients undergoing immunosuppressive drug therapies.

Another major component of the InterCEDD review is the report of the evaluation of the potential therapeutic application of the unique South African plant, *Sutherlandia frutescens* subspecies *microphylla* (SFsm) by our South African colleagues Nigel Gericke, Carl Albrecht, Ben-Erik van Wyk, and Bani Isaac Mayeng. There are again serious and verifiable anecdotal evidence to suggest a positive effect on AIDS patients and the major attributes of the plant drug have been highlighted in this review. The use of SFsm in South African traditional medicine dates back to antiquity but it remains a highly prized ingredient today in folk medication throughout South Africa. Sutherlandia was used as a convalescent tonic in South Africa during the 1918 'flu pandemic, and is still traditionally used to treat 'flu. The plant contains L-Canavanine, a compound that had previously been patented for its antiviral activity, including against influenza virus and retroviruses, including HIV (Green, 1988.)[9]. The usually very high yield of this substance in SFsm may be responsible for the impressive anecdotal evidence in AIDS therapy. SFsm also contains Pinitol, a known anti-diabetic agent (Narayanan, 1987)[10], has been isolated from *Sutherlandia* leaves, and quantitative work is in progress. A US Patent (Ostlund, 1996)[11] suggests that pinitol may have clinical application in treating the wasting in cancer and AIDS patients. Interestingly Sutherlandia has historically been used to treat wasting illnesses, including TB. According to Gericke and his colleagues, a high quantity of GABA was isolated from dry *Sutherlandia* leaves in levels up to 14 mg/g dry weight. This inhibitory neurotransmitter could account for the use of the plant for anxiety and stress and depression, and for the improvement in mood and well being experienced by patients taking *Sutherlandia*..

Oral dosage forms of the phytomedicine have already been formulated, crop domestication has been conducted and the plant-drug is listed in the post-conference consideration for advanced development.

Herbal Medicinal Products for Opportunistic Infections

The advent of HAART has contributed to a remarkable decline in HIV associated morbidity and mortality. Clinical observations of spontaneous remission of previously untreatable opportunistic infections in subjects on HAART reflect the substantial degree of immune reconstitution, which can be achieved with this therapy. Despite the progress made in the use of these potent anti-retroviral drug regimens in the suppression of HIV-viremia, antiretroviral therapy is not able to achieve a complete reconstitution of the immune system in advanced HIV-infected patients. In fact, a complete normalization of HIV associated immunological alterations has not been reported so far, but the observation period of subjects on potent antiretroviral therapies is still relatively short. The situation is further complicated by occurrence of "immune reconstitution syndrome" in patients in the early phases of treatment with HAART who develop tuberculosis, *M. avium* complex, and

[9] Green. M.H. (Filed Jan 25, 1988) Method of treating viral infections with amino acid analogs. United States Patent 5,110,600.

[10] Narayanan, et al. (1987) Pinitol – A New Anti-Diabetic compound From the Leaves of *Bougainvillea Spectabilis*. *Current Science* **56**(3), 139-141

[11] Ostlund, R.E and Sherman, W.R (Filed March 4, 1996). Pinitol and derivatives thereof for the treatment of metabolic disorders. US Patent 5,8827,896

cytomegalovirus disease. In addition, drug therapy can be limited over time by side effects and emergence of drug resistance. These considerations have evoked growing interest in the development of specific drugs for the treatment of these opportunistic infections associated with HIV/ AIDS. In developing countries, the high incidence of parasitic infections contributes significantly to the high mortality recorded among AIDS patients in developing countries. Plants have been the source of many drugs used in current use for the treatment of protozoal diseases. Evaluation of plants used in traditional medicine in Nigeria and Cameroon for the treatment of parasitic diseases lead to the identification of several compounds with potential for the treatment of malaria, leishmaniasis, trypanosomiasis and opportunistic infections caused by *Cryptosporadium parvum* and *Toxoplasma gondii*. Indole alkaloids, protoberberines, indoloquinoclides, and pregananes are among the most promising chemotypes. Some of the active plant extracts obtained from *Picralima nitida, Cryptolepis sanguinolenta, Chasmanthera depedens* and *Dracania mannii* are candidates for possible development as phytomedicines containing mixture of active molecules in a standardized dosage form. Most of the points raised above for malaria apply equally for other parasitic infections.

For anti-fungal activity, the review specifically highlighted the following plant medicines (among others) for serious consideration:
Aframomum spp.
Cassia alata
Bridelia ferruginia
Dracaena mannii

Our previous report on the biological activity of the Dracaena saponins indicates possible applications in a variety of opportunistic infections[12]. Pharmacognostical profile for Aframomum Cassia and Bridelia are included in the Handbook of African Medicinal Plants[13]. For possible anti-tuberculosis activity, the review specifically highlighted the following plant medicines (among others) for serious consideration:

Buddleja cordada subsp. Cordata
Tinosporin (*Tinospora cordifolia*)
Sutherlandia frutescens subspecies *microphylla*
Berberine containing plants.

For the treatment and management of opportunistic infections, it has been suggested that prophylaxis against Mycobatrium avium can safely be withdrawn or withheld in adults with HIV infection who experience increase in $CD4^+$ cell count while receiving antiretroviral therapy[14]. Since the use of a prophylactic against this opportunistic infection has been associated with remarkable survival benefits, it may be useful to evaluate the usefulness of Tinosporin or other *T. cordifolia* preparations as a transitions medication for patients who are no longer on azithromycin, clarithromycin or rifabutin, the antibiotics preferred as prophylactic agents. Although the anti-tuberculosis activity of extracts of *T. cordifolia* has been confirmed by several blind clinical studies[15],

[12] Okunji, C.O. *et al*. (1996) "Biological Activity of Saponins from Two Dracaena species", *Adv. . Exp. Med. Biol*.: 404: 415-28.
[13] Iwu, M. (1993) Handbook of African Medicinal Plants, Boca Raton, CRC Press. pp434.
[14] Currier, J. S. *et al*. (2000) Discontinuation of *Mycobatrium avium* Complex Prophylaxis in Patients with Antiretroviral Therapy-Induced Increase in $CD4^+$ Cell Count," Annals of Internal Medicine. 133(7): 483-503.
[15] Rege, N. *et al*. (2000) Lecture at the 3rd International Congress on Phytomedicine, Phytomedicine, Suppl. II: 56.

the exact mechanism of action of the plant-drug is not known. The plant is a known immuno-potentieting agent[16] and has been shown to modulate nitric oxide synthesis in mouse macrophages[17]. Jackson (see plenary session) at this conference has also presented potential interaction between AIDS and Leishmaniasis and summarized the on-going work by our group and others to develop appropriate phytomedicines based on traditional medicine.

Perhaps the conclusion from the InterCEDD review of herbal medicinal products for HIV/ AIDS and malaria is the need for continual monitoring of these potential medicinal agents, with critical but open-minds, so that successful therapies can be made available to a larger population of patients, especially those living in developing countries who can not afford the high cost of synthetic medication. As we observed in a recent communication[18]: "Traditional medicine is not an alternative to modern medicine, but a complement. Although the precise mechanism of the observed effects may still not be properly understood, therapeutic synergism will eventually be achieved through parallel practice and research."

[16] Kapil, S. and Sharma, S. (1997) Immunopotentiating Compounds from *Tinospora cordifolia*, *J. Ethnopharmacol*. **58**(2): 89-95.

[17] Yokozawa, T. *et al.* (1999) *Tinospora tuberculata* Suppresses Nitric Oxide Synthesis in Mouse Macrophages, *Biol. Pharm. Bull.* **22**(12): 1306; see also Rege *et al* in note above.

[18] Iwu, M. M. and Gbodossou, E. (2000) "The Role of Traditional Medicine", The Lancet, 356(1) Perpectives p.3.

APPENDIX A
QUESTIONS AND COMMENTS MADE DURING THE PLENARY DISCUSSIONS AND PAPER PRESENTATION

Plenary Session Presentations, Paper Presentations and Poster Presentations

Track A: Policy Issues, Regulations and General Overview

Robert Lettington	ICIPE, Nairobi, Kenya
Tony Onugu	BDCP, International
Ibrahim Abdu-Aguye	NIPRD, Nigeria
Tunde Ahonsi	The Ford Foundation, Nigeria, USA

Track B: Recent Advances in Traditional Interventions Systems for HIV/AIDS

Joan Jackson	Walter Reed Army Institute of Research, USA
Caroline Weishaupt	Alternative Therapy for HIV/AIDS
Joe Sodipo	Center for Integrative Medicine & Research, Lagos, Nigeria
Louis Barrows	University of Utah, Dept. of Pharmacology and Tox., USA

Track C: Recent Advances in Traditional Medicines for Malaria

Marie-Annick Mouries	TDR, WHO, Geneva
Edith Ajaiyeoba	University of Ibadan, Nigeria
Chris Okunji	BDCP/WRAIR, International
Oliver K. Wasem	CIPKA, S.A., Switzerland

Track D: Standardization and Evaluation of Traditional Medicines

Karnyius Gamaniel	NIPRD, Nigeria
Elijah Sokomba	BDCP, Lagos, Nigeria

Track E: Protocols for Clinical Research

Paul Akubue	InterCEDD, Nsukka, Nigeria
Erik Gbodossou	PROMETRA, Senegal

Track F: Creating, Enhancing and Maintaining Collaborative Research

Contributed **Paper Presentations**

Odiri Onoruvwe	University of Jos, Nigeria
Moges Kassa	Ethiopian Health and Nutrition Research Institute
Ifeyinwa Flossy Obuekwe	University of Benin, Nigeria
Hellen A. Oketch-Rabah	University of Kenya
Idowu Olanrewaju	RITAM, Clinical Development Group
Jacob J. Abdullahi	Winners Medical Diagnostic/Herbal Centre
Ted Emanuel	Jamaica Naturopathic Physicians Regulating Council

Poster Presentations

M.C.Maduereira	Center of Malaria and Other Tropical Diseases, Portugal
Abigail Olu Imogie and Ifeyinwa Flossy Obuekwe	University of Benin, Nigeria
Angela Duncan Diop, Chioma Obijiofor and Maurice M. Iwu	BDCP, International
Chris Okunji	BDCP/WRAIR, International

Special Guest Presentations

Patti Boulaye	Support for Africa 2000, England

TRACK A: OVERVIEW, POLICY ISSUES AND REGULATIONS

The following is a brief synopsis of each plenary discussion and key points raised by the speaker. Questions and important statements have also been included to provide some insight upon some of the important issues raised during the conference.

Robert Lettington, ICIPE, Nairobi, Kenya

Robert Lettington, started by asking the question of whether or not local level knowledge fits into the framework of intellectual property rights (IPRs)? He proceeded to give an overview of various bodies like TRIPS and WIPO (Trade Related Aspects of Intellectual Property Rights and World Intellectual Property Organization) that are looking at these issues, and he also gave brief explanations of specific legislations that have been made, including the Peruvian Draft Legislation and the Philippines Legislation. Mr. Lettington then proposed possible ways to deal with all these IPR issues. He suggested using the parts of the IPRs that can be beneficial, like a combination of trade secrets and petty patents, which can be cheaper.

Jeremy Job: How do you assess the integrity of IPR bodies?

Robert Lettington: If the question is whether or not certain Intellectual Property (IP) offices will be doing it for the wrong reasons, try to concentrate on how they are applying their standards. Really try to lobby and pay close attention. IP offices also know that they are new to these issues, and you can easily detect wrongdoing. Even the big IP offices have had problems, and there are cases when people get patents turned over.

Innocent Ononiwu: It is costly to attain a patent, so how do I do it if I do not have the money?

Robert Lettington: A short-term solution is that you do not have to pay to establish your trade secret. However, you do have to determine what it is that you want, in terms of your product. Patents give you the most expensive monopoly. It is specific to each case, many people want to avoid patents, but they may need it to reproduce a product, or to decide where it will be marketed.

Tony Onugu, BDCP, Nigeria

Tony Onugu, explained that the Fund for Integrated Rural Development and Traditional Medicine is a method that the BDCP has developed under the sectors of capacity building and benefit sharing. This trust fund is an end product of their efforts to integrate conservation, drug development and the socioeconomic well being of communities. Continuing, he noted that the process of benefit sharing starts first by creating relationships with traditional healers, and with the appropriate recognition of all parties contributing to the development of a therapeutic agent. Mr. Onugu also called attention to different challenges they had with the project. He explained that there is a continuous need to have closer coordination with local, national and international institutions, and they also learned not to limit themselves to one organization when securing additional funds. The final challenge he stated was to position the Fund to act as an intermediary for lending and benefit sharing activities through micro-credits.

Tunde Ahonsi: What are you plans for sustainability?

Tony Onugu: As one of the start-up phases of the fund we tried to get into the money market by dispersing money as a means to generate extra capital for the continuation of the project, and in doing this we tried to involve as many organizations a possible.

Maurice Iwu: Would it be good if traditional healers themselves organized a fund like this?

Tony Onugu: Yes this is an idea we are entertaining, by giving out small loans to traditional healers to help them develop their products. This was involved with the micro-credits, which create a way for the traditional healers to help pay back and gain from the system they helped create.

Ibrahim Abdu-Aguye, Nigeria

Ibrahim Abdu-Aguye, reported that because failure of the control programmes within Nigeria, the diseases of HIV/AIDS and malaria are on the rise. When there is a lack of clarity and legislation in policies this leads to failure in control programmes. He also noted that when there is a lack of human, financial and provisional support policies fail. Poor information, education and communication on policy and activities can also lead to problems. In relation to drug development the World Health Organization (WHO) is stepping up to the challenge. WHO/Madagascar has made a formal adoption of scientific procedures for the evaluation of traditional medicines. He went on to explain that nothing can be taken for granted there must be policy on product regulatory authorities on procedures for registration of traditional medicines, prompt registration of products that are ready for the market and bioresources exploration and exploitation with respect to medicinal plants, animals and minerals. In closing he also provided the recommendations that there must be policy on IPRs and benefit sharing among individuals, families, households and communities.

Elizabeth Kafaru: Let us focus on what we experience in the field and what the government says that is never verified. You say you are preventing HIV by giving condoms, but you are corrupting society. You are the scientists, is it true that you can stop AIDS with condoms?

Abdu-Aguye: The HIV epidemic is so huge that we can only do the best we can. Protected sex with condoms is much safer than un-protected sex, thus it would be wrong for a government not to promote condoms. Nothing is 100%, but we are coming up with new solutions.

Elizabeth Kafaru: In regards to malaria, there are lots of traditional medicines used, and if you concentrated hard you could have something in the market soon because most of what we use are weeds. Secondly, if you recognize us then why do you not let people choose where they are treated?

Abdu-Aguye: According to the WHO there are only four countries (China, North and South Korea and Vietnam) where there is full integration of traditional and orthodox medicine in all aspects of health care and where there is transfer from one system to the other. The important step is to have regulation--we have started the process of integration here in Nigeria, but we are unfortunately still in the process of legislation. Even for the conventional medical practitioner we must know what service or benefit he provides, thus first I must know about the traditional healer before I can send someone there to receive treatment.

Tunde Ahonsi, Ford Foundation

Tunde Ahonsi, began by stating how pleased he was to be involved in this conference. At the Ford Foundation we believe that the diseases of HIV/AIDS and malaria are a call for multiple responses

and full multisectoral approach. He then noted that in view of all of the developments that have been made on the continent and the accessibility of traditional healers to ordinary Africans we have no choice but to develop new preventions and traditional treatments for these diseases. At the Ford Foundation we hope that this conference will speed up the process and translate all of this quickly into local medicines that are easily accessible.

TRACK B: RECENT ADVANCES IN TRADITIONAL MEDICINE INTERVENTION SYSTEMS FOR HIV/AIDS

Joan Jackson, Walter Reed Army Institute of Research, USA

Joan Jackson, commenced by explaining the opportunistic disease Leishmania. Mrs. Jackson then proceeded to tell the relevance of this study at this conference. With the re-occurring leishmanial disease problems there has been new interest in traditional medicinal therapies. She noted that they have learned a considerable amount from traditional healers. This work has had at its foundation ethnomedical knowledge, followed by laboratory analyses, then back to the parasites' physiology and nutritional requirements, and finally, to a working hypothesis of how some of the herbs kill the Leishmania by disruption of their lipids. She closed by describing the strategy they used to carry out this research. With the information they had, they took a Federal Drug Administration (FDA) approved drug to verify their hypothesis of how the natural products work. They thought that if they used the FDA drugs with the already existing patents then they would be able to afford to work and make progress, and the second-generation drugs would be the natural drugs.

Elijah Sokomba: Have you tried the drug to see that it actually interferes with the Leishmanial cells?

Joan Jackson: They have looked at various, non-positive compounds and it was possible to watch the decomposition. They will go into a dog trial during the next year and with that they will know if their hypothesis is true. We did it this way to bring in long-term revenue, and the new use of an already existing drug would do this.

Caroline Weishaupt, Alternative Therapy for HIV/AIDS, Switzerland

Caroline Weishaupt started by giving a synopsis of the clinic where she works. She explained how they look at the organism as whole, and an outbreak is connected to a way of life that can open doors to opportunistic infections. Maintaining a good quality of life is the ideology behind their treatments. Almost sixty to eighty percent of their patients use their treatments alone. With all of their treatments they try to adapt them to the way the patient is feeling. She closed by explaining various treatments they use which are developed at their clinic and elsewhere in Europe. Many of their recipes come from Tibetan Refugee recipes that have been known for about twenty years.

Joe Sodipo, Centre for Integrative Medicine and Research, Lagos, Nigeria

Joe Sodipo began his presentation on integrative management for HIV/AIDS by stating that if the truth were known there are probably more people dying of the treatments for HIV/AIDS than the disease. He then explained that at his center they believe that the integration of western medicine with natural medicine is the answer to AIDS therapy. The role of nutritional deficiencies and poverty cannot be ignored as well as their actions on the immune system, which, in particular, cause the body to be left open to a debilitating series of opportunistic infections. He further expressed concern by noting that proper nutrition should be the main focus of integrative management of HIV/AIDS, rather than the use of retro-viral agents. He then gave some examples of integrated management, which consists of medicinal plants with healing properties such as probiotics, anti-microbial, anti-fungal, anti-septic, anti-viral and anti-inflammatory, antioxidant nutrients as well as good natural nutrition. Prof. Sodipo closed by presenting four HIV positive case studies. Despite the good results from the case studies, they do not claim to have cured AIDS, but they will claim that they can give patients a better quality of life.

Innocent Ononiwu: How long were the people treated from the case studies? It would also be interesting to have data on the HIV levels. What happened to the parameters you used initially?

Sodipo: The study has all taken place during the last three years, and all of the patients are still alive except the older male patient. In relation to the HIV levels, this has been a challenge throughout our studies. Most patients say that they already feel so weak they are afraid that if their blood is taken again they will feel even weaker.

Yahaya Sekagya: Your paper is good. The initial studies are difficult, and what we need to do is help Prof. Sodipo develop a better analysis model. As we criticize we must also try to help and improve.

Louis Barrows, University of Utah Dept. of Pharmacology and Toxicology, USA

Louis Barrows presented the research he is doing with an ICBG project for the establishment of the CEM-TART assay for screening of traditional medicine for anti-HIV activity. Mr. Barrows started by stating that it is estimated that over 22 million people in sub-Saharan Africa are infected with HIV, which probably amounts to 70% of the disease incidence worldwide. The truth is that doctors here have probably been treating AIDS for a long time. He then explained that the overriding goal of the ICBG project is to increase the net worth of West-Central African forests as living resources and to demonstrate the feasibility of using drug development as an incentive for the conservation of biological diversity. Therefore, in order to work towards this goal, the ICBG has established a whole virus-based "CEM-TART" assay for the screening of traditional anti-infective medicines. He concluded by drawing attention to a few conclusions that were drawn from the studies; that whole virus assays have been developed to allow testing of plants extracts for anti-HIV activity, that this technology allows us to test the hypothesis that phytomedicines used traditionally for HIV and other infectious diseases will have direct anti-HIV activity; and that with this system we should be able to know whether or not these plant-based treatments can kill HIV/AIDS.

Jean Emile Njab: 1) I would like to hear more about the virus immunocontainment of the disease? 2) And what sort of equipment is necessary for this sort of testing?

Barrows: 1) This a period when there is very low production of the virus, along with very low levels of CD4, and eventually the patient will no longer be able to produce the virus and then the patient will start suffering from complications of the disease. This system does not focus on this part as a distinguishable state. They are still producing viruses. 2) Unfortunately this sort of equipment is very costly. To begin with you need an inverted condenser microscope ($2,000), safety cabinet, incubator, various other miscellaneous supplies and the ability to make a *su culture* medium etc… However, there are possibilities out there in terms of funding. Fogarty has an AIDS grant limited to $30,000 US dollars a year that any collaborating entity can apply for.

Seitz Renate: How many tests does it take to do one screening?

Barrows: We can do a positive control along the side of each test, and as far as how many we can do at one time, well we have one technician and we can do 6-8 in one day. If you take some controls away, then it would take about 20 different setups in one day.

TRACK C: RECENT ADVANCES IN TRADITIONAL MEDICINES FOR MALARIA

Marie-Annick Mouries, TDR, WHO, Geneva

Marie-Annick Mouries explained that many of the WHO drug research projects focus on natural plant research, because of primary drug related medical needs. Primary health care in developing countries call for drugs that are not complicated by multi-drug resistance, they must be short course oral treatments and have a low cost per treatment (approximately US $1). She then stated that the normal drug discovery process is unfortunately very long and complicated. It begins with compounds/chemistry libraries, primary *in vitro* assay, hits, secondary *in vitro* assay, leads, lead optimization, biopharmacy (development abilities) tertiary assays and development candidates. Conversely, Mouries continued by explaining that the route to herbal medicine development may be more beneficial and quicker. For example, herbal medicines are affordable and they are locally available to endemic areas. She ended her presentation by noting that the WHO's herbal medicine strategy is to first confirm the efficacy of the medicine, optimize and standardize herbal preparation for local use, and identify and synthesize active constituents by lead optimization programs to enable the identification of novel drugs.

Prof. Ekwenchi, Chemist from the U. of Jos: When we talk about resistance, how can we have a drug that works for so many people and then there are cases in which nothing will work for a specific person?

Mouries: We must be able do a test on field strength. The resistant panel for a particular patient may be a special specific resistant strength. My personal point of view is that if you are convinced of an extract, then it is possible to use this extract, however, nothing can ensure that it will work for every patient.

Edith Ajaiyeoba, University of Ibadan, Nigeria

Edith Ajaiyeoba began her presentation by explaining that due to the continuing interest of the University of Ibadan in antimalarial drug development from Nigerian ethnomedicine, a university team carried out two ethno botanical surveys on the use of traditional herbs in the management of fever in two southwestern Nigerian communities. Ajeiyeoba went on to explain that out of 514 traditional healers, herbalists, elders and mothers interviewed they encountered ordinary fever most commonly along with Hot Body fever, Yellow fever, Fatique fever, Rain fever and Headache fever. They determined that there were sixty-eight different recipes used to treat all of these febrile illnesses, and each recipe was composed of two to six different herbal ingredients. In conclusion, she stated that various studies are being carried out on some of these herbal recipes in the efforts to improve them and ensure safety.

Sekagya: Have you worked with the traditional healers on the results? I recommend that you have training with the traditional healers to help them diagnose properly.

Ajaiyeoba: Normally we go back to the traditional healers and talk to them about their work, and on this particular occasion they asked if they could study with someone else so we trained them and showed them how to measure weight loss etc… We help them as much possible because we are in this together.

Chris Okunji: We have talked about a number of different recipes today, and I would like to know how many recipes you have all together?

Ajaiyeoba: We have almost 106. It has nothing to do with number; this was just the way I decided to propose the information to you today.

Chris Okunji, BDCP / Walter Reed Army Institute of Research (WRAIR)

Chris Okunji began his presentation by stating that as a part of ongoing research collaboration between the ICBG and the BDCP, an *in vitro* screening programme was initiated to discover both plant extracts and new natural product compounds as potential antimalarial agents. He went on to explain that most of the research is done at the WRAIR, but the extracts come from Nigeria and Cameroon. Dr. Okunji continued by giving a brief overview of how the *in vitro* test works and also how the antimalarial data and chemical informatics are stored in the Chemical Information System (CIS) at WRAIR. He concluded his presentation by noting that all of the plants tested have been used for treatments of malaria in Africa, and for the most part the compounds that show activity are of the greatest concern. The importance of this data is that activity has been seen and out of 720 samples from forty-seven plant families tested for antimalarial properties, fifty-five percent showed remarkable activity.

Innocent Ononiwu: I would like to know if you have handled the molecules that had operational activities?

Okunji: No, we have only completed the first screening stage, and we have done synthetic testing. Next we will do the pharmacological testing.

Oliver K. Wasem, CIPKA S.A., Switzerland

Oliver K. Wasem began by giving an overview of the company CIPKA S.A., Switzerland that collaborates with teams of researchers from all around the world. This company works to create links with people that have had positive results by exploiting patents and sponsoring research in the field of natural therapies. Mr. Wasem described the product Gadelpas that they have developed for malaria. He stated that clinical tests were carried out on thirty patients, and seventy-two percent of the cases were cured in three days. He finished his statement by expressing that they are so impressed with how much Africa has done with so little especially coming from a place where they have so much but do so little.

Robert Lettington: I am not against Intellectual Property Rights (IPRs) immediately. If you are getting information from other communities why do you need a patent? It seems like you are just wasting money.

Wasem: There are two sides to everything one is that here in Africa there may unfortunately be a gap in the process from extraction to standardization and maybe we serve as a bridge to continue the process. The IPR is something that can make this possible. We want something that can be applicable so that it can be brought back to where it came from.

Gabriel Ajudi: Is this a way of attaining a free license? And furthermore, some of us are frustrated; we cannot see who wants to help and who does not. Give the communities a job to do themselves, if it will be protected and be a Nigerian product with the help of the Swiss, it should be exported from Nigeria.

Wasem: First of all this is not a way of attaining a free license. This is a method that can enable accessible prices. We can create a free market for Africa this way, by selling the product at a higher price abroad this can be possible. We want to be able to get as much from this side (the Industrialized World) as we can to make it more accessible, because accessible pricing can create a free market for Africa. In response to your second question, people see Africa as not having the capacity to do this, but we see this as a faster way to let them do it.

Maurice Iwu: In terms of IPRs, a disease like malaria, the issues are not that simple. The intellectual rights can remain with the traditional healer forever but the medicine should be shared and the benefits will be for the common good of the entire continent of Africa and even all the malaria endemic countries. We should think about ways to optimize the value of the resources, the whole income, we must add value to these herbs. If there are so many anti-malarial treatments out there we have to start using them.

Wasem: You may be concerned that when there is an agreement with the people where you have taken information what will happen when there is a gain, what has been done for the people? Thanks to the patent and the protection of the IPR there is nothing taken away from Africa. Through the help of Prof. Wambebe we want to reward the source of the knowledge. Africa and the people who are suffering are our priorities and we want to provide a product for the people who need it the most. We know something about the question of integrity, and when we go to a place where there is knowledge, our role is not to take it away. We want to create a reality that is possible and get it to as many people as possible.

TRACK D: STANDARDIZATION AND EVALUATION OF TRADITIONAL MEDICINES

Karnyius Gamaniel, National Institute of Pharmaceutical Research and Development, Nigeria

Dr. Karnyius Gamaniel discussed his opinions on the issues of standardization and evaluation of traditional medicine, and he stressed that standardization is fundamental to the issue of developing traditional medicines. He went on to explain that once you have guaranteed safety, or regulation specific standards, the provision of a monograph is a requirement. For the most part herbal medicine must have a process of identification and documentation, but regrettably many rural traditional healers do not have this understanding. He then noted that the government has increased the balance used to fight against HIV/AIDS and malaria, and traditional medicine is a concern right now, so we must take advantage of the opportunity. However, acceptability is the big question among traditional healers. Seventy percent of herbal practitioners are not accepting standardization. He then explained that first we must convince traditional healers of the benefits of standardization and then we must develop a systematic trail in terms of collection, pre-clinical validation and clinical validation as a way to confirm traditional claims. In closing, Dr. Gamaniel stated that if there is a system of standardization adopted for dosages it could very easily revolutionize traditional medicine by creating a more accessible market.

Yahaya Sekagya: You started in the middle of the process of standardization by starting with the state of collection. There are many other things that need to fit into the plan: the altitude, the time of the day, the temperature… Many of us think that we have control over something, but we do not. There are microclimate changes that are very important. In Ethiopia there is a tree where traditional healers must do a ceremony before they start. The ceremony is a detailed review of the system; this plant is an endangered species. Thus this serves as a mode of conservation. They concentrate different chemical concentrations by allowing the plant to dehydrate when a drought is coming, and two weeks later they extract the plant. They have standardized this process. I wonder at what level there is a need for us to understand the processes of the complete process.

Gamaniel: We are not saying that their methods are not standardized. For example, in Germany and the United Kingdom they have worked to standardize traditional medicine. They know that what the people did was traditional, but they have improved it with clinical evaluation methods. I had a man come to the office with a packet of herbal medicine that he pretended to measure, but when I measured what was there I realized that he had tried to do it using a western method. Let us use the traditional way, but we must develop some universal guidelines.

Elizabeth Kafaru: We have water-based remedies that can be so strong they affect the container. With lie callus bitters for example, we have seen that you cannot put it in plastic. We used to use calabashes to prepare medicines until aluminum was introduced, which we used for a while until we learned that it can contribute to the growth of cancer cells. We know these things because traditional healers have standardized and kept records. In this practice this knowledge will arise, and based on the reaction we will know what kind of container to use.

Elijah Sokomba, BDCP, Lagos, Nigeria

Elijah Sokomba began his presentation by stressing the importance of herbal medicine and the necessity of regulations derive from the need to safeguard against public health issues regarding

quality, safety and efficacy of products. He then gave some examples of regulation and control that have been established elsewhere. Prof. Sokomba then went on to give some other reasons for regulations that are often overlooked. For example, it should be done for the reasons of research, development and conservation. Traditional healers should be motivated to work on conservation activities to make certain that they do not run our of their raw materials, and education and training will complement the traditional medical knowledge that is passed from one generation to the next.

Yahaya Sekagya: I find that there is a lot of selfishness. There is an increasing shift from orthodox to traditional and this is creating a place for understanding, but who is going to benefit? Are they looking to see if it is safe for us? We have to concentrate on whether or not it is safe for all of the classes even the low-income classes.

Robert Lettington: There is a lot of discussion about information that must be submitted, and with this is there a problem with confidentiality? Do you have to surrender confidentiality?

Sokomba: The documents are submitted in trust. The standard operating procedure is that all information is kept very classified.

Mwananyanda Mbikusita Lewanika: I would like to forget that I came to Nigeria and heard traditional medicine referred to as unorthodox, it should be the orthodox medicine, and normally it is referred to as alternative medicine.

TRACK E: PROTOCOLS FOR CLINICAL RESEARCH

Paul Akubue, International Center for Ethnomedicine and Drug Discovery, Nigeria

Paul Akubue presented a paper on an approach for a rapid clinical evaluation of traditional medicines for efficacy and safety in HIV and malaria. He started by giving an overview of the intimidating and costly process of drug development, and then he declared that given this information it is necessary to come up with a shorter program. Prof. Akubue then began explaining his approach. First it is necessary to find traditional healers and patients who are willing to cooperate. First confirm that the patient has malaria and then give the patient the traditional medicine that hopefully he has taken before. If he takes it, and there are no side effects and the malaria goes away then we can confirm efficacy. However, how do we confirm safety? Before the healer gives the medication he checks organs and vital signs, and in this case there are also no ethical questions because the patient is someone who normally takes this particular medication. He then stated that with HIV/AIDS this approach is a little more difficult but still possible. In conclusion, Mr. Akubue noted that this approach is meant to speed up the process and enable traditional healers to market their products in the country.

Louis Barrows: If these studies are to be accepted by the National Food Drug Administration and Control (NAFDAC) then there would probably be a required number? How many and do you think there is significant historical data for comparison?

Akubue: I cannot answer for NAFDAC, but if it is for malaria, traditional healers can use the treatments on a wide population very easily. It is likely that every time you do it, you will probably get the same result. Whether NAFDAC will accept it I do no know. A control is not necessary because you do not need someone who has not taken the drug. You only want the results before and after so no placebo is necessary.

Emanuel Bader: We know that malaria treatment is not a prolonged treatment; I would like to know what precautions you took to make sure it was safe. I am curious about the methodology you use, because you are developing this for society.

Akubue: You modify the procedure how you think you should. If they have a prolonged effect, then ask them to come back, and you will consult them. You monitor the patients and take necessary action if anything arises.

P.A. Uche: These drugs do not come down from heaven; orthodox medicines are still herbs from nature. It just depends on the mode. Some people want to draw a line between synthetic and those that come from plants.

Akubue: Yes, Quinine, the initial drug used for malaria is a good example in that it is all a question of synthesis.

Erik Gbodossou, Association for the Promotion of Traditional Medicine (PROMETRA), Senegal

Erik Gbodossou spoke about PROMETRA and about the Traditional Experimental Treatment Center he works with in Senegal. First, Mr. Gbodossou gave a synopsis of the way they run their clinic in Senegal. The clinic has both a physician and traditional healers, but the traditional healers do all of the consulting and treating. In March 2000 the distribution of patients according to results,

were that nineteen percent had net improvement, .6% had no response, one percent had stagnation and 79.4% had full recovery. He went on to express that what is important is that there is improvement. For example, with their HIV treatment program used on ten patients after five months there was no stagnation and all the patients were cured or felt better. In conclusion, Mr. Gbodossou said with urgency, it is important for Africa to understand that the world is speaking about traditional medicine, and Africa must take advantage of this and be proud. Africa must work towards the recognition of traditional medicine in all African countries. We must encourage and support traditional healers organizations.

Rosy McNeil: I think that it is wrong to say that everything physicians say is correct, and I do not want us to focus on you verses me or practical medicine verses voodoo. I am not against traditional healers, but what is wrong with learning a little physiology? How can we collaborate if the basic principles are not the same?

Gbodossou: I am a French speaker and you are an English speaker, and if we make an effort to understand each other, then we can share.

CONTRIBUTED PAPER PRESENTATIONS

Odiri Onoruvwe, The University of Jos

Odiri Onoruvwe presented the data that the University of Jos collected through the ethno-botanical survey, pharmacological studies and preliminary clinical evaluations of medicinal plants in the treatments of HIV/AIDS. She began by stating their first objective to document the ethno-medical data on various potions used by traditional healers to treat HIV/AIDS. She continued with the second objective by explaining that with the 500 patients that opted for traditional treatments for HIV there was evidence of slight weight gain, improved appetite, increased strength and improved CD4 counts. They also used mice in a pilot test to watch for signs of toxicity with certain potions. Mrs. Onoruvwe wound up the presentation by noting that they were able to determine that certain potions were safe and that some did have appetite-increasing affects along with blood pressure lowering abilities.

Moges Kassa, Ethiopian Health and Nutrition Research Institute

Moges Kassa, began by giving an overview of the malaria problem in Ethiopia. He stated that malaria effects seventy-five percent of the population. Over the last forty years chloroquine has been the number one treatment, but unfortunately now Chloroquine resistant *Plasmodium falciparum* exists all over the country. Due to the magnitude of the problem they turned to plants with the hopes of developing a treatment that would be less toxic, more effective, cheap and locally available. In order to carry out this research they developed an *in vitro* test for anti-malarial activity of extracts of reputed medicinal plants against *P. falciparum*. Mr. Kassa then gave a summary of the procedures and the plants used during the *in vitro* testing.

Mrs. Renate: Are these plants widely grown in Ethiopia?

Kassa: Yes they are.

Louis Barrows: Are these plants normally used as teas?

Kassa: Yes, most of them were tested based on their traditional use.

Ifeyinwa Flossy Obuekwe, University of Benin, Nigeria

Ifeyinwa Flossy Obuekwe, began her presentation by explaining that traditional medical practices still remain at the forefront of primary health care for Africans, and then she explained a study a team from the University of Benin did to examine promising traditional remedies in current use for the management of malaria in a rural community. One hundred and fifty rural dwellers ages twenty to seventy were used as respondents. Eighteen types of traditional remedies were used by the respondents and it was established that traditional medicines was preferred to orthodox drugs by about 86.7 percent because it is more effective (sixty percent), cheap (eighty-five percent) and locally available (95.6 percent). She then provided several recommendations that were made after the study. For example, traditional medicine must be considered as a main therapy, there needs to be new initiatives in the fields of economics and social research to be established because there is inadequate information available. Also that it is a public health responsibility to ensure safety and there was also evidence that people will abandon traditional practices if they are shown that they can be harmful. Furthermore, she stated that traditional healers should be trained and not criticized by orthodox practitioners. In closing, she declared that in seeking a sustainable solution to the issues of health and well-being, it is necessary for every culture to take stock in ancient wisdom and remedies as possible answers to present problems.

Kennedy Chah: You said that we must rely on traditional medicine for the treatment of malaria. How were these studies done? Can you compare the treatments?

Obuekwe: Yes you are correct, this is only the first step. We wanted to know what people were using. Malaria is an endemic problem here. The respondents said that when they take orthodox medicines they have certain symptoms, and when they take traditional medicine they are usually cured.

Hellen A. Oketch-Rabah, University of Kenya

Oketch-Rabah began by giving an overview of the study that was done by a large group from the University of Nairobi scientists, the Chemistry Department at the University of Kenya and the Ministry of Health of Kenya. She explained that the study was carried out among populations who still use traditional medicine in their communities. The main objectives were to carry out a rapid assessment of the community knowledge and perception of malaria, and also to tap into the indigenous knowledge. The methods used were a questionnaire suited to the objectives, a process of random sampling of seventy-three respondents from three sub locations and interviews that were done to learn about the therapies used. Mrs. Oketch-rabah offered that the specific outputs from the study were documentation of indigenous knowledge regarding the use of plants to cure malaria, and a report describing the community's knowledge and perception of malaria. From a list of plants they developed, it was possible to select ten plants that were most widely used and to understand how they were administered. In closing, she explained that the research team hopes to work with the traditional healers again in regards to certain potions they were able to identify, because through the study it became clear that the healers have a diagnosis that is relevant and the treatments conform to what is in the literature, thus they can be used as phytomedicines themselves.

Abigail Imogie: Since they are working on the same type of project at the University of Benin, Nigeria, I would like to have a collaboration between East and West Africa to help us meet our goals.

Idowu Olanrewaju, The RITAM Clinical Development Group
Olanrewaju, started by explaining how and why the Research Initiative on Traditional Antimalarial Methods (RITAM) was developed. Then he offered that it was formed in 1999 and now has over 100 members in thirty countries, there is a partnership between the World Health Organization (WHO) and GIFTS () of Health, and there is a network of all those working on traditional herbal remedies. He then proceeded to given an overview of the clinical studies that they have done along with a brief description of the guidelines and methods of standardization they use. In conclusion, Wilcox claimed that they have found that clinical observations on traditional remedies are feasible and useful, that standard operating procedures are needed to ensure quality of studies and that standard operating procedures have been proposed. The standard operating procedures should also be further developed with input from all other interested parties so that they can be widely accepted, and it should be decided whether or not these standard operating procedures could be published as a joint WHO/AFRO/RITAM document when they are agreed upon.

Jacob J. Abdullahi, Winners Medical Diagnostic Centre
Jacob J. Abdullahi, presented upon Winniecure, which is an HIV/AIDS herbal treatment that has been patented in Nigeria. It has been characterized and evaluated for efficacy against HIV/AIDS. Winniecure was used with a total of 1,335 HIV/AIDS patients, which were monitored for the disappearance of opportunistic infections and improvement in their overall health status within a two-year period. He then went on to explain that 1,305 patients (97.8 percent) who completed the therapy responded positively while thirty (2.2 percent) died within a period of five to eight weeks. Abdullahi also gave a brief synopsis of retrospective studies and other specific tests that were carried out to monitor the status of the patients. In closing, he noted that the Winniecure treatment is a very important milestone for Nigeria and the global fight against HIV/AIDS.

Ifeyinwa Flossy Obuekwe: During the treatment of those who had TB, you stated that it was cleared within two months, but I do not understand this because TB is bacterial, and HIV 1 and 2 are viral?

Abdullahi: This was a discovery along the way, because we did not develop a drug to be anti-bacterial.

Ted Emanuel, Jamaica Naturopathic Physicians Regulating Council
Ted Emanuel, spoke about using a holistic approach to life. He explained that each patient is uniquely different and they must be treated this way, and accordingly, those that have a weakened immune system generally share the same dietary tendencies like the over-consumption of sweets, fruits, milk, refined flower products, yeast and other processed foods. Mr. Emanuel said that it is important to eat properly to avoid weakening the organs. In conclusion, he reiterated this by claiming that if we are going to give people in need something, then it should something that is natural and good for them. Give them proper nutrition by the means of education.

Idris Amaka, University of Jos: I heard Ted make the statement that fruits and fruit juices were bad, can you elaborate on this? And what are the nightshade plants you referred to?

Emanuel: God created Fruits, but the over-consumption of fructose has a centrifugal energy to disperse things. It is poison and it destroys vitamins and minerals. Nightshade plants are tomatoes, potatoes, eggplant, peppers as well as other plants that originated in a tropical climate.

Grace Olarewaju Martina: In this part of the world our food is based on carbohydrates, so how can we apply this to Africa?

Emanuel: In Africa, we need to focus on wholesome grains, not refined grains. Vegetables are also very important, but also look at the beans and peas that exist around you because they have very high amounts of minerals and proteins. Also try not to eat fish, and if you do eat fish eat smaller fish. If you eat poultry make sure it was raised by yourself and not imported or raised in mass. And furthermore, watch the amount of food you eat and do not eat late at night, because this will attack your immune system.

PRESENTATIONS MADE BY SPECIAL GUESTS

Patti Boulaye, Great Britain

Patti Boulaye, a Nigerian singer, who lives in Britain and works with the organization Support for Africa, explained that her organization would like to have more collaboration between African traditional healers and African scientists. Support for Africa wants to help maximize the benefits that Africans can derive from their communities. She then stressed the importance of getting more participation by helping people to understand that this particular problem will be an economic risk in the future.

APPENDIX B
THEMATIC WORKING GROUP SUMMARIES

SUMMARIES FROM THE THEMATIC WORKING GROUPS

After the conclusions of the plenary presentations, Prof. Iwu expressed his hopes that together the conference participants would be able to come up with some sort of declaration. He requested comments on the InterCEDD reports on herbal medicinal products for HIV/ AIDS and malaria. He explained that submissions have already been made by South and Central Africa, but not a lot of input has been made by East and West Africa. We also need to have submissions of plants by individual countries, workshops on African herbal remedies, review and selection of medicinal plants to make an African bank of medicinal plants, preparation of monographs by an expert panel and the production of a directory of African herbal remedies. Prof. Iwu then proceeded to invite volunteers from Africa and abroad from all disciplines to sign up to get this process started. A working group was eventually established by nominations and individual volunteers to serve as a study group to work with InterCEDD and BDCP towards the implementation of some of the recommendations of the thematic working group.

Summarized below are the deliberations of the participants of the four thematic working groups, which met throughout the conference. The groups were asked to discuss the issues surrounding their theme, come up with practical solutions and expected outcomes. During the group presentations a communiqué was also made concurrently to speed up the development of a declaration.

Group A: Malaria

The participants of the malaria group began by stating that traditional medicine and malaria have a long history together, but the partnership of traditional medicine with other areas of health care is not a full one.

The suggested solutions are as follows:

1) That the government must recognize traditional medicine, because it is already a part of health care.
2) A project team should be established to improve medical practices in the areas of documentation because a lot of traditional medical clinics do not have good documentation.
3) This team could also provide training in basic pharmaceutical practices in the clinics.
4) They could also provide workshops geared to airing some of the traditional healers ways to enhance their profession and gain more acceptance.
5) The project team should come up with a way to validate traditional medicine and address issues of standardization.

Some of the expected outcomes were that if the above areas are focused on during a 1-5 year period there will be serious acceptance to traditional medicine in every country, and this would be very beneficial to the patient. There will be the developments in the areas of speeding safety and standardization up with respect to malaria. Traditional medicine will reach a much higher level, i.e. there will be students, well kept records and there will be communication between different networks.

Group B: HIV/AIDS

The participants of the HIV/AIDS working group discussed the issues of epedimeology, diagnosis, treatments, social and economic effects, transmission, education, nutrition, government policy, co-infection, ignorance, culture, fatalism and secrecy.

The practical solutions they declared were: immunosystem boosting because there are traditional remedies that are capable of enhancing the immune system, which should be properly screened. Awareness and training, which should take care of issues raised under ignorance. Also a good system of communication should be established between health workers, the government and policy makers, which will eventually enhance the activities of traditional healers. As a final point research activities in herbal remedies should be well coordinated to avoid research duplication, conserve funds and harness results.

The proposed expected outcomes are as follows:

1) That traditional healers organize themselves, so as to speak with one voice.
2) Adequate respect should be given to traditional healers.
3) The practice of traditional medicine should be legalized.
4) Practical and positive collaboration should exist between traditional healers and others involved in traditional medicine that shall facilitate research efforts, trust and collaboration among scientists, traditional healers, policy makers, local communities and funding agencies.
5) The expected period of treatment with herbal medicine should be three years to take care of incubation periods.
6) Adequate funding should be made available for research in herbal medicine.
7) The remedies for HIV management should take care of opportunistic infections.

Group C: Policies

The problems and issues surrounding policies were the recognition that traditional medicine should be addressed as alternative medical system to the conventional western-based medicine. A lack of clarity exists because traditional healing continuously has a low status because it does not receive the support (financing, laboratories for testing etc…), which it needs. Another problem that exists is the transposing from one system into another; for example, there is a need to develop a system, which grows from the practice itself instead of trying to transpose ideas from orthodox medical practices. Furthermore, the system should be more flexible; governments should not set impossible standards since the use of alternative medicine in Africa is usually a matter of life and death unlike in the Western world where it is seen as a subsidiary issue. Laws should be used to encourage and not necessarily as an instrument of punishment. And finally, there is a need for Alternative Medicine Practitioners realize that standardization is in their own interests.

Proposed suggested outcomes are as follows:

1) To use a bottom up approach instead of making policies and trying to force them upon people.
2) Traditional healers should be encouraged to give their own ideas and then such ideas should be developed into laws and policies.
3) Healers should come together and fashion out a Code of Ethics.
4) Healers should form a Professional Association to regulate their profession.

5) Regarding IPRs there is a need to integrate international protocols into our national laws to ensure that plant and animal species are adequately protected.
6) Local communities should benefit when things are extracted from their communities.

Group D: Standardization and Development of Herbal Medicines for HIV/AIDS and Malaria

The group that worked on standardization declared that standardization is the process of producing a product with some quality, efficacy and safety anywhere using the same materials. However, not all aspects of traditional medicine can be standardized because of cultural differences that affect the practice of traditional medicine. Unfortunately, of present there is little or no formal standardization of herbal medicines in African countries. Due to the fact that the potions of traditional practitioners are used beyond the locality of the practitioner there is a great need for the standardization of their products. The group then went on to suggest specific areas of herbal medicines that should be standardized as the proposed expected outcomes.

The proposed expected outcomes are as follows:

1) At the source there should be identification of the plant, the plant part and cultivation is suggested to ensure uniform collection of plants.
2) For the collection and pre-treatment of the plant materials, the time of collection (year, month and time of day), and the drying methods used should be documented.
3) In terms of the method of preparation, consistent measuring aids should be used, and the method of processing and preparation should be consistent and clearly stated.
4) For the packaging and storage this should take into consideration environmental hazards such as effects of moisture and light, transportation hazards such as handling, shelf life and the packaging should protect against contamination.
5) The product should be able to withstand all of the above and the labeling should follow already established regulations on packaging of conventional medications.
6) The dosage and modes of administration must be well defined.
7) There should be well-defined measurable parameters for assessing the efficacy of the potion within a stated period of time.
8) Product safety should pass some form of toxicological analyses.

APPENDIX C
FULL TEXT OF THE COMMUNIQUE

COMMUNIQUE

The diseases of Malaria and HIV/AIDS continue to cripple the continent of Africa. Traditional medicine is a tremendous untapped resource for addressing these health crises. While many research institutions and independent investigators in Africa have reported positive clinical outcomes in the use of traditional medical remedies for the treatment of HIV/AIDS and malaria, their results have not led to significant contributions in either drug development or treatment of disease. The nature of these health crises combined with the availability of traditional medicine create a clear need for immediate action, therefore the Conference:

ACKNOWLEDGES the lack of significant progress towards legal recognition of traditional medicine as an integral part of the health care system, against the background that it represents a primary health care system, not merely a lifestyle.

RECOGNIZES that central to worldwide acceptability of traditional medicine is the need for appropriate standardization of herbal remedies, subject to cultural differences and modes of practices.

FURTHER that standardization be specific to areas of identified need, including;
–Source of the medication, pretreatment, mode of collection, preparation, packaging, labeling, storage, dosage and route of administration.

SUGGESTS that there should be defined measurable parameters for assessing efficacy of remedies within a stated specified period of time.

FURTHER suggests that safety parameters must be standardized following the usual acceptable toxicology methods.

ACCORDINGLY, government policy should grow from traditional medical practice and not seek to transpose from orthodox medicine.

SUGGESTS that weaknesses in the practice of, and research on, traditional medicine, reflect a need for local capacity building, including documentation, organizational capacities and networking.

THUS, a need exists for an institutional unit or nexus to drive coordinated future action.

APPENDIX D: Working Papers and Reference Materials Distributed at the Conference

1. Andrew Sparber, Jacqueline C. Wooton, Larry Bauer, Gregory Curt, David Eisenberg, Tina Levin, Seth Steinberg (2000) "Use of Complementary Medicine by Adult Patients Participating in HIV/AIDS Clinical Trials". *Journal of Alternative and Complementary Medicine*, **67(**5) 415-422.

2. Gesa Matthee, Anthony Wright and Gabriele Konig (1999). HIV Reverse Transcriptase Inhibitors of Natural Origin. *Planta Medica* **65** 493-506

3. A.J. Vlietinck, T. De Bruyne, S. Apers and L.A. Pieters (1997). Plant-Derived Leading Compounds for Chemotherapy of Human Immunodeficiency Virus (HIV) Infection. Plant Medica 64 pp. 97-109.

4. World Medical Association Declaration of Helsinki (2000): "Ethical Principles for Medical Research Involving Human Subjects". The New Helsinki Declaration

5. A Renewed Assault on an Old And Deadly Foe.. *Science* v. **290**. 20 Oct. 2000.

6. U.S. Congressional Record: Proceedings and Debates of the 106th Congress, Second Edition. Report of the BDCP International Conference on Ethnomedicine and Drug Discovery.

7. A Model Clinical Protocol for the Evaluation of Plant Medicine with Potential for the Treatment of HIV/ AIDS. Adapted from Bastyr University Protocol Report, parts 1-7 by Dr. Lisa Messerole.

8. Malaria – A WHO information booklet for schools.

9. Commercial Production of Indigenous Plants as Phytomedicine and Cosmetics – A BDCP Press publication.

10. Synopsis of the InterCEDD Review of Herbal Antimalarial Agents.

11. Synopsis of InterCEDD/BDCP Review of Plant Antiviral Agents and Herbal Medicinal Products for Opportunistic Infections in HIV/ AIDS

APPENDIX E: Model Protocol for the Clinical Evaluation of Herbal Medicinal Products

Phase I Clinical Trial of Agent X
MEDICAL HISTORY FORM

PATIENT IDENTIFICATION: _____ Date _____
Investigator:_____
(To be filled out by investigator)

Birthdate:_____Race:_____Sex:_____
(To be filled out by patient: Confidential)

If you are HIV positive, please begin with section I and answer all sections. If you are HIV negative, answer section II only.

I. HIV History: Please answer the following questions to the best of your ability.

First positive test for HIV (the AIDS virus)?_____CD4 count (if known) _____

When do you think you were first infected with HIV (your best guess)?_____

Of the following possible ways that HIV may be transmitted, which one(s) have applied to you? (Check each line that applies to you)

_____ Sexual contact with men

_____Sexual contact with women

_____Sharing needles for injection drug use

_____Blood transfusions

_____Treatments for Hemophilia

_____Occupational exposure as a health care worker

_____Other risk factors or possible ways you became infected with HIV (please specify):

_____

II.Current Symptoms or Health Conditions: Please check "no" if you do not currently have the symptom or health condition. Check "yes" if you currently do have the symptom or health condition. Then assign a number from 1 to 10 to indicate the severity of the symptom.
(1 = very mild; 10 = very severe)

constitutional
no yes score (1-10)

__ __ ___ fatigue
__ __ ___ fever
__ __ ___ night sweats
__ __ ___ weight loss
__ __ ___ loss of appetite (anorexia)
__ __ ___ malaise

skin
no yes score (1-10)

__ __ ___ rashes
__ __ ___ itching
__ __ ___ dry
__ __ ___ Kaposi's sarcoma
__ __ ___ shingles (Herpes zoster)
---- ---- ------ diagnosed fungal infection
(mouth, buttocks, genitalia, other)

Do you currently have or have you had allergies to Drugs/ Medications/ Food or Environmental factors? Please list these allergies:

_____ _____ _____ _____

PATIENT IDENTIFICATION: _____Date _____ Investigator:_____

II. Please check "no" if you do not currently have the symptom or health condition. Check "yes" if you currently do have the symptom or health condition. Then assign a number from 1 to 10 to indicate the severity of the symptom. (1 = very mild; 10 = very severe)

lymph nodes

no yes score (1-10)

__ __ ___ swelling (enlargement)
__ __ ___ pain

eyes

no yes score (1-10)

__ __ ___ vision changes
__ __ ___ spots in front of eyes (floaters)
__ __ ___ light sensitivity (photophobia)

oral

no yes score (1-10)

__ __ ___ canker sores (aphthous ulcer)
__ __ ___ painful/bleeding gums)
__ __ ___ thrush (Candida yeast)
__ __ ___ Kaposi's sarcoma in mouth
__ __ ___ oral Herpes
__ __ ___ oral hairy leukoplakia
__ __ ____ red or sensitive tongue
___ ___ ___ rash/irritation @ mouth corners or nose folds

respiratory

no yes score (1-10)

__ __ ___ cough
__ __ ___ shortness of breath
__ __ ___ nasal congestion
__ __ ___ sinus congestion
__ __ ___ phlegm
__ __ ___ wheezing
__ __ ___ painful breathing

gastrointestinal\abdominal

no yes score (1-10)

__ __ ___ nausea
__ ___ ___ vomiting (>1/week)
__ __ ___ pain
__ __ ___ bloating
__ __ ___ pain when swallowing
__ __ ___ difficulty in swallowing
__ ___ ___ undigested food in stool
__ __ ___ constipation
__ __ ___ poor appetite
__ __ ___ diarrhea

genitourinary

no yes score (1-10)

__ __ ___ discharge from penis/vagina
__ __ ___ decreased sex drive
__ __ ___ ulcerations
__ __ ___ genital warts (Condyloma)
__ __ ___ genital Herpes
__ __ ____ genital candida or yeast
__ __ ___ increased menstrual periods (length)
__ __ ___ increased bleeding during menstrual period
__ __ ___ loss of or decreased bleeding during menstrual period

rectal

no yes score (1-10)

__ __ ___ warts
__ __ ___ rectal Herpes
__ __ ___ hemorrhoids
__ __ ___ cut or tear (fissure)
__ __ ___ bleeding
__ __ ___ itching

musculoskeletal

no yes score (1-10)

__ __ ___ joint pain
__ __ ___ joint stiffness
__ __ ___ swollen joints
__ __ ___ muscle pain
__ __ ___ muscle loss

PATIENT IDENTIFICATION: _____Date _____ Investigator:_____

II. Please check "no" if you do not currently have the symptom or health condition. Check "yes" if you currently do have the symptom or health condition. Then assign a number from 1 to 10 to indicate the severity of the symptom. (1 = very mild; 10 = very severe)

neurological
no yes score (1-10)

__ __ ___ headaches
__ __ ___ confusion
__ __ ___ poor short term memory
__ __ ___ numbness in hands & feet
__ __ ___ seizures or convulsions
__ __ ___ weakness in arms and/or legs
__ __ ___ tingling and/or burning sensation
__ __ ___ black-outs
__ ___ ___ other

psychological
no yes score (1-10)

__ __ ___ apathy/loss of interest
__ __ ___ mood swings
__ __ ___ depression
__ __ ___ anxiety
__ __ ___ anger bursts
__ ___ ___ other

III.Current and Past HIV-Related Problems and Symptoms: Please answer the following questions for the period covering *the past 6 months* **and whether you are** *EXPERIENCING THE SYMPTOM TODAY*. In the ***past six months***, have you had *any* of the following problems or symptoms?

	Problem present in the past 6 months?		Problem lasted more than two weeks?		Problem there now?	
Problem	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
a. Persistent fatigue (feeling tired all day long) for at least 3 consecutive days.						
b. A new skin problem or infection that lasted for at least 3 consecutive days.						
c. An unusual bruise or bump or skin discoloration that lasted at least two weeks.						
d. Diarrhea for at least 3 consecutive days.						
e. Persistent or recurring fever higher than 100° F for at least 3 consecutive days.						
f. Tender or enlarged glands or lymph nodes for at least 3 consecutive days.						
g. Persistent, frequent or unusual headaches for at least 3 consecutive days.						
h. Drenching sweats at night on at least 3 occasions.						

Patient Identification:_____ Date:_____ Investigator:_____

III. Please answer the following questions for the period covering *the past 6 months* **and whether you are** *EXPERIENCING THE SYMPTOM TODAY*. In the ***past six months***, have you had *any* of the following problems or symptoms?

Problem	Problem present in the past 6 months?		Problem lasted more than two weeks?		Problem there now?	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
i. Thrush (Candida), or white patches in your mouth or throat.						
j. Canker sores (mouth, lips or tongue).						
k. An unintentional weight loss of 10 pounds or more (unrelated to dieting or exercise).						
l. Burning, tingling, or sensitivity in the feet for at least 3 consecutive days.						
m. Aching or soreness in legs for at least 3 consecutive days.						
n. Frequent tripping, stumbling, or falling						
o. Difficulty getting up from a chair or toilet (needing to use your arms to get up).						
p. Difficulty in your hands, handling objects, or with handwriting.						
q. Poor memory or memory loss.						
r. Problems with concentration or attention.						
s. Loss of vision or blurred vision.						

t. Have you had any other symptoms related to HIV infection? Circle: **Yes** **No**

If YES, List them:

u. Have you had any other symptoms NOT to HIV infection? Circle: **Yes** **No**

If YES, List them:

PHASE I CLINICAL TRIAL OF Agent X
MEDICAL OUTCOME SURVEY(MOS) FORM

Patient Identification:_____Date:_____Investigator:_____

The following questions concern your health status. Please circle one number on each line.

1.Limited for more than three months
2.Limited for three months or less
3.Not limited at all

limited
limited less **than 3 months**
more than 3 months

I. Has illness due to HIV limited you in:

a. The kinds or amounts of vigorous activities you can do like lifting heavy objects, running or participating in strenuous sports: 1 2 3

b. The kinds or amounts of moderate activities you can do like moving a table, carrying two full bags of groceries or bowling: 1 2 3

c.Walking uphill or climbing 10 steps without resting: 1 2 3

d.Bending lifting or stooping: 1 2 3

e. Walking one block: 1 2 3

f. Eating, dressing, bathing, or using the toilet: 1 2 3

g. Have you been unable to do certain kinds or amounts of work, housework, or schoolwork because of your health? 1 2 3

Patient Identification:_____Date:_____Investigator:_____

II. The following are questions about your feelings. Please circle one number on each line.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

	All	Most	Good bit	Some	Little	None
a. During the past month, how much of the time has your health limited your social activities (like visits with friends or relative)	1	2	3	4	5	6
b. During the last month, how much of the time have you felt very nervous ?	1	2	3	4	5	6
c. During the last month, how much of the time have you felt calm and peaceful?	1	2	3	4	5	6
d. During the past month, how much of the time have you felt downhearted and blue?	1	2	3	4	5	6
e. During the past month, how much of the time have you been a happy person?	1	2	3	4	5	6
f. During the past month, how often have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6

III. In general, would you describe your health as: (Circle one response)

1.Excellent 2.Very Good 3.Good 4.Fair 5.Poor

Patient Identification:_____Date:_____Investigator:_____

IV. In this section, please circle the number that describes whether each of the following statements is more true or more false for you.

1.Definitely true
2.Mostly true
3.Not sure
4.Mostly false
5.Definitely false

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a. Your health is excellent.	1	2	3	4	5
b. You are as healthy as anybody you know.	1	2	3	4	5
c. You are somewhat ill.	1	2	3	4	5
d. You have been feeling bad lately.	1	2	3	4	5

V. In the past month, have you had any bodily pain? (Circle one answer) Yes No

a. If yes, was the pain : (Circle one answer)

1.Very Mild 2.Mild 3.Moderate 4.Severe

b. If yes, where was / is the location of the pain:_____

Agent X Clinical Trial Patient Monitoring Report Form (by phone if possible)

Patient ID_____ Study day #__ Interviewer____ Date____/

1. Has there been any change in your daily or weekly regimen (diet, nutrition, exercise, stress level, sleep pattern, etc) since your last clinic visit with study staff?
___No ___Yes If yes, explain:_____
_____
_____
_____
2. Has there been any change in the way you are taking the study medication?
___No ___Yes Explain_____
_____
_____
3. Has there been any change in any of your treatment, medicines or supplement program outside of this study?
___No ___Yes Explain_____
_____
_____
_____
4. Is you general health: __Better __Worse ___No change?
_____
_____
_____
5. Are you having any problems or have you questions with the study protocol?
___No ___Yes Explain_____
_____
_____
6. Is there anything else you think I should know that I haven't asked?
___No ___Yes Explain_____
_____
_____
_____
7. As a reminder your next appointment for:
a clinic visit (with a fasting blood draw/with a MOS questionnaire)
a phone interview
[fill in as appropriate for the upcoming visit or phone contact]
is _____. Please remember to bring in your study medication, diary, (the completed MOS form if appropriate), and -if there has been a change in brand or formula - your vitamins, supplements and any none study medications at your next clinic visit.

Phase I Clinical Trial of Agent X
LAB FLOWSHEET

_____

PATIENT IDENTIFICATION:

DATE								
Albumin								
Albumin								
Alkaline phos								
BUN								
Calcium								
Chloride								
Cholesterol								
Creatinine								
GGT								
Glyco HB								
Glucose								
Iron								
LDH								
Phosphorous								
Potassium								
Protein								
SGOT (AST)								
SGPT (ALT)								
Sodium								
Total bilirubin								
Triglyceride								
Uric acid								
BUN/Creat ratio								
Alb/glob ratio								
HDL								
LDL								
RBC count								
Hematocrit								
Hemoglobin								
Total WBC count								
Platelet count								
RDW								
MCV								
MCH								
MCHC								
Neutrophil-segs								
Bands								
Monocytes								
Eosinophils								
Basophils								
Lymphocyte								
ESR								
CD4 cell count								
CD8 cell count								
CD4/CD8 ratio								
NK cell count								
B cell count								
Comments								
Initials								

cr: \ dataform \ misc \ labflow

LAB FLOWSHEET Page 2

_____

PATIENT IDENTIFICATION:

DATE								
URINE								
Color								
Clarity								
pH								
Specific gravity								
Protein								
Glucose								
Ketones								
Bilirubin								
Urobilinogen								
Blood / Hgb								
Nitrates / l esterase								
HIV viral RNA								
PN355 levels								
Comments								
Initials								

cr: \ dataform \ misc \ labflow

A Program of Study on Agent X

Research Institute

Table of contents

LITERATURE REVIEW

Introduction

The nature of Agent X

Agent X as a medicinal plant and therapeutic agent

Known Components of Agent X and Relevance to immunomodulation, anti-HIV or other therapeutic mechanisms

PLAN FOR FURTHER STUDIES

I. *In vitro*

A. Effect studies

1. **a.** Antibiotic properties.

b. Comparison of antibiotic properties vs. other antibiotics

2. Anti-viral activity

Since anti-viral activity is very important to the eventual economic potential of Agent X, the assays should be carefully chosen and executed. Common assays involve plaque or titre reduction in cell culture. Preparation of the material for anti-viral assays is critical. Preferably no solvents other than physiological buffer solutions should be used. A battery of several viral types may be most useful: Herpes simplex and the adenoviruses for the DNA viruses; polio, vesicular stomatitis, measles, hepatitis, HIV for the RNA viruses, etc.

Anti-HIV activity is a measure of the degree of protective effect exerted by a test agent against the AIDS virus' cytopathic effect on T-lymphocytes. A test substance is considered active if it affords 100% protective at two or more concentrations ($1/2 \log_{10}$), moderately active if the protective effect exceeds 50% in two concentrations or 100% in one concentration. Among types of natural products that have shown frequent anti-HIV activity are sulfated polysaccharides.

Unfortunately, the National Cancer Institute has recently suspended its program of testing for anti-HIV activity. They will soon implement a new program based on several particular mechanisms of HIV inhibition. We should find a laboratory, which will do the older assay for gross activity against HIV as we are unsure of the potential mechanism. We have located two laboratories, which can do mechanism-based assays. One is of especially great interest as its assay is for a substance's influence on the infectivity of the virus, including cell adhesion and penetration. This is highly relevant to Agent X's suspected mechanism of action. The other laboratory's assay is an enzyme-based test of anti-retroviral activity (the virus' ability to take over cell reproductive machinery)..

While we have focused on anti-HIV activity, other viral studies also should be done.

3. Anti-adhesive properties

4. Immunomodulation

B. Constituent analysis

1. General constituent analysis

Characterization of the entire crude extract may prove to be of value in pursuing protection of the invention. This may be done through a HPLC (high pressure liquid chromatography) fingerprint or TLC (thin layer chromatography) with photographs of the chromatogram. These analyses are readily available at commercial laboratories. In relation to potential toxicity, testing for heavy metals or pesticide residues may be useful.

2. Identification of bioactive constituents

In order to identify active constituents, positive bioassays are needed first. Then, then a trial and error of different extraction techniques is done, followed by repetition of the of the fractions. A combination of separation and assay methods, such as the bioautographic assay (overlaying a TLC plate on HSV-1 infected monkey kidney cells) may speed the identification of active ingredients. When irreducible active fractions are identified, toxicity and other in vitro or clinical work may be repeated on fraction.

II. Animal studies

A. Effect studies

1. Anti-microbial

Animal studies of anti-microbial activity, if done, should be developed from *in vitro* work and depend on the existence of a good model for the relevant condition.

2. Immunomodulation

B. Toxicity

Acute toxicity in groups of 10 rats over two weeks with high doses of Agent X administered by gavage with observation for changes in behavior or health or death costs about $2000. No necropsy or organ examination is done. Intermediate term (3 month) toxicity studies of rats with larger numbers and post-mortem pathological examination of liver, kidney, and brain is in the area of $20,000 to $50,000.

III. Clinical studies

Initial studies in humans are typically for toxicity. We suggest the following Phase I studies.

First, a toxicity test of 6 weeks in 5 HIV negative volunteers with a battery of lab work and pre- and post-study physical exams and health-related quality of life assessments. Volunteers would receive an escalating dose of Agent X: Thus the final dose would be twice the therapeutic dose. Exclusion criteria would include impaired #####, Lab work would include chemscreen and CBC. Immunomodulatory tests would include lymphocyte populations, phagocytosis

This would be followed by an open trial in 10 HIV positive patients for a minimum of 60 days with potential extensions depending on outcome. Principal outcome measures would be viral load and CD4+ lymphocyte counts. Inclusion and exclusion criteria would be established in conjunction with the investigators and sponsors

If there are suggestive results in this clinical work, a phase II study in three groups as suggested by would be indicated. This study would compare Agent X versus the full protocol i and the other treatment components versus a placebo.
Human studies must be approved by the Institutional Review Board before subjects are recruited.

TIMELINE FOR PRIORITY ITEMS

LEGAL, CONTRACTUAL, AND ADMINISTRATIVE ISSUES

BUDGET ESTIMATES AND FINANCIAL ARRANGEMENT

STUDY PROTOCOL: Agent X

Short title: Phase I Clinical Trial of Agent X

Title:

Principal investigators:

Sponsor:

Table of Contents

1. Summary and schedule of events:

Schedule of events

Day of Study:	-7	0	7	14	21	28	35	42	49	56	63
Visit number	1	2	3	4	5	6	7	8	9	10	11
Activity											
Phone contact											
Informed consent			*								
Medical Hx			*								
Physical exam											
MOS											
Sx assessment											
Prov meds/direct.											
Patient observ.											
Pill count											
CBC											
Chemscreen											
Lipids											
Urinalysis											
ESR											
Lymphocyte panel											
Viral load											

2. Introduction

Lymphocyte panel:
- CD_4 +T cells (total and relative),
- CD_8+T cells (total and relative)
- NK cells
- CD_4/CD_8 ratio
-B cells (total and relative)

Complete blood count:(CBC)

- Leucocytes	($1/mm^3$)
- Erythrocytes	($10^6/mm^3$)
- Thrombocytes	($10^3/mm^3$)
- Hemoglobin	(g/dl)
- Hematocrit	(%)
- MCH	(pg)
- MCV	(fl)
- MCHC	
- Monocytes	(%)
- Lymphocytes	(%)
- Bands	(%)
- Polymorphs	(%)
- Eosinophils	(%)
- Neutrophils	(%)
- Basophils	(%)
ESR	mm/hour

Blood Chemistry:

Albumin/gloulin	ratio
Total Bilirubin	mg/dl
Direct Bilirubin	mg/dl
Alkaline phosph.	units/L
SGPT (ALT)	units/L
SGOT (AST)	units/L
LDH	units/L
BUN	mg/dL
Creatinine	mg/dL
Glucose	mg/dL
Gycolated Hb	
Uric Acid	mg/dL
Cholesterol	mg/dl
Calcium	mg/dL
Phosphate	mg/dL
Total Protein	g/dL
Albumin	g/dL
Sodium	meq/L
Potassium	meq/L

Total CO_2	meq/L
GGT	U/L
LD	U/L
Triglycerides	mg/dl
Lipids	
HDL	mg/dl
LDL	mg/dl

Routine Urinalysis
Color
Clarity
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood/Hgb
Nitrates/Leukocyte esterase
Microscopic exam

Voluteers who meet study criteria will be called to make a baseline appointment.

Day 0 - Baseline visit (visit 2)

A physical exam will be performed. A baseline Medical Outcome Study (MOS) questionnaire will be completed. In HIV subjects, 7 ml. of blood will be drawn for viral load and sent to Labcore for analysis. A urine specimen for routine urinalysis will be requested from the patient. Patients will be instructed in the medication regimen and given their medications for the week. Patients will take the first dose of their medication at the clinic and remain at the clinic under observation for the first two hours to monitor possible toxicity reactions.

During the interim between Day 1 and Day 7 (approx. day 3), the patient will be contacted by phone by a research team member to check on his/her health status, concommitant medications, adverse reactions, to reinforce compliance, and to remind the subject of the next appointment on day 7.

Day 7- visit 3

On Day 7 of the study, the subject will have a brief physical exam including weight, blood pressure, temperature and heart rate. A review of adverse events, concomitant medications and compliance will be completed. Twenty ml. of blood will be drawn for CBC, Chemscreen. Blood for CBC, and Chemscreen along with the urine will be sent to the laboratory for analysis. Medications remaining from the first week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the second week and reinstructed on compliance with the protocol.

Day 14-visit 4

On day 14 of the study, a review of adverse events, concomitant medications and compliance will be completed. Medications remaining from the second week will be collected. The subject will be supplied with sufficient medication for the third week and reinstructed on compliance with the protocol.

During the interim between Day 14 and Day 21 (approx. day 18), the patient will be contacted by phone by a member of the research team to check on their health status, concommitant medications, adverse reactions, to reinforce compliance, and to remind the subject of the next appointment on day 21.

Day 21-visit 5

On Day 21 of the study, the subject will have a brief physical exam including weight, blood pressure, temperature and heart rate. A review of adverse events, concomitant medications and compliance will be completed. A MOS questionnaire will be completed. Medications remaining from the third week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the fourth week and reinstructed on compliance with the protocol.

During the interim between Day 21 and Day 28 (day 24), the patient will be contacted by phone by a research team member to check on their health status, concommitant medications, adverse reactions, to reinforce compliance, and to remind the subject of the next appointment on day 28.

Day 28-visit 6

On Day 28 of the study, the subject will have a brief physical exam including weight, blood pressure, temperature and heart rate. A review of adverse events, concomitant medications and compliance will be completed. Twenty ml of blood will be drawn for CBC, Chemscreen. A urine specimen for routine urinalysis will also be requested from the patient. Medications remaining from the fourth week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the fifth week and reinstructed on compliance with the protocol.

Day 35-visit 7

On day 35 of the study, a review of adverse events, concomitant medications and compliance will be completed. Medications remaining from the fifth week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the sixth week and reinstructed on compliance with the protocol.

During the interim between Day 35 and Day 42 (approx. day 39), the patient will be contacted by phone by a research team member to check on their health status, concommitant medications, adverse reactions, to reinforce compliance, and to remind the subject of the next appointment on day 42.

Day 42-visit 8

On Day 42 of the study, the subject will have a brief physical exam including weight, blood pressure, temperatue and heart rate. A review of adverse events, concomitant medications and compliance will be completed. An MOS questionnaire will be completed. Medications remaining from the third week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the fourth week and reinstructed on compliance with the protocol.

During the interim between Day 42 and Day 49 (approx. day 45), the patient will be contacted by phone to check on their health status, concommitant medications, adverse reactions, to reinforce compliance, and to remind the subject of the next appointment on day 49.

Day 49-visit 9

On Day 49 of the study, the subject will have a brief physical exam including weight, blood pressure, temperature and heart rate. A review of adverse events, concomitant medications and compliance will be completed. Twenty ml of blood will be drawn for CBC, Chemscreen. A urine specimen for routine

urinalysis will be requested from the patient. Medications remaining from the seventh week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the eighth week and reinstructed on compliance with the protocol.

Day 56-visit 10

On day 56 of the study, a review of adverse events, concomitant medications and compliance will be completed. Medications remaining from the eighth week will be collected and compliance will be assessed. The subject will be supplied with sufficient medication for the ninth week and reinstructed on compliance with the protocol.

During the interim between Day 56 and Day 63 (approx. day 60), the patient will be contacted by phone by a research team member to check on their health status, concomitant medications, adverse reactions, to reinforce compliance, and to remind the subject of the next appointment on day 63.

Day 63-visit 11

On Day 63 of the study, the subject will have a physical exam. A review of adverse events, concomitant medications and compliance will be completed. A MOS questionnaire will be completed. Thirty ml of blood will be drawn for CBC, ESR, Chemscreen with lipids, lymphocyte panel, and viral load. A urine specimen for routine urinalysis will also be requested from the patient. Medications remaining from the ninth week will be collected and compliance will be assessed.

7. Stipend

8. Compliance

Subjects enrolled in this study will be outpatients, and the assurance that the subject took the medication as perscribed will be very important. The investigator will select those subjects who have the ability to understand and follow instructions and display a willingness to adhere to the treatment plan. At each visit, the subject will return the remaining study medication and diary, so that compliance can be estimated from the remaining quantity. Compliance will be monitored and reinforced at every visit and phone contact.

9. Target parameters

Primary outcome variables:

Adverse events on therapy including:

- new signs or symptoms
- significant increases in severity of present signs or symptoms
- significant changes in lab tests from baseline
- significant changes in MOS scores
- Lymphocyte sub-populations:
- CD4+ lymphocytes (total and relative)
- CD8+ (total and relative)
- CD4+/CD8+ ratio
- NK- cells
- B cells (total and relative)

Viral load (HIV branched chain DNA or mRNA PCR) in HIV positive subjects

Secondary outcome variables:

10. Adverse events

Adverse events for this purpose are all disorders of well being, subjective and objective disease symptoms, intercurrent illnesses and accidents occurring in the course of the clinical study. Adverse events on therapy will be rated for severity by the PI as mild, moderate, serious, or toxic (resulting in morbidity or mortality). The causal relationship to the study medication will be rated as possible, probable, definite or unknown.

The occurrence of serious or worse adverse events must be immediately reported by phone by the investigator/principal investigator to co-investigators and to the sponsor.

Payment for care for adverse events causally related to the study medication is to be the responsibility of the study sponsor.

11. Criteria for discontinuation

11.1 Criteria for discontinuation of the individual patient

- hospitalization during the observation period and discontinuation of the test medication
- appearance of symptoms of intolerability
- patient's refusal to further participate in the trial

11.2 Discontinuation criteria for the entire study

Should serious adverse events occur plausibly related to the administration of Bercedin, the principal investigator in conjunction with the co-investigators will decide after consultation with the patient, on the discontinuation of the study.

12. Documentation and evaluation

12.1 Case report form

A case report form (CRF) will be prepared by the investigators. All data referring to the history, physical examination and test parameters will be recorded on this CRF. Adverse events are to be recorded on the respective pages of the CRF.

12.2 Amendments to the protocol

Amendments to the protocol by the investigator are not permitted once the protocol has been approved by the investigators, the sponsor, and the Bastyr University IRB. If an amendment to the protocol should be necessary, the investigator/principal investigator will inform the IRB Chair and enclose the amendment as appendix with the study protocol after consultation with the monitor.

12.3 Statistical planning and evaluation

The incidence of adverse events for each dosage level in both HIV negative and positive subjects will be reported and analyzed in a exploratory fashion. Baseline and dose level termination changes

as well as baseline to medication termination changes in CD4+T lymphocytes, CD8+T lymphocytes, NK-cells, B cells and viral load will be analyzed by parametric methods and others, as determined appropriate (ANOVA...)

13. Ethics

13.1 Ethical guidelines

The clinical trial will be carried out in accordance with the guidelines of the Declaration of Helsinki and the Belmont report. The trial must be approved by the Bastyr University Institutional Review Board and its guidelines followed.

13.2 Patients' informed consent

The investigator will be responsible for preparing the informed consent document. The investigator will use information provided in the Clinical Investigator's Manual to prepare the informed consent document.

The informed consent document will be used to explain, in simple terms, before the subject is entered into the study, the risks and benefits to the subject. The informed consent document must contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time.

In addition to the elements required by all applicable laws, the following two paragraphs must be included in the informed consent document. The language may be altered to match the style of the document, provided the meaning remains unchanged.

1) "I understand that the persons in charge of this study (may stop the study or stop my particpation in the study at any time, for any reason, without my consent."

2) "I hereby give permission for the persons in charge of this study to release the information regarding, or obtained as a result of my participation in this study to #####including its agents and contractors, and allow them to inspect all my medical records associated with this study, except that my identity will remain confidential, except that they will be provided as noted above or as may be required by law."

13.3 Withdrawal from the study

A subject may end the participation in a clinical study at any time without specifying any reasons. However, if a subject withdraws prematurely from the study, the investigators will make a reasonable effort to find out the reason for his or her withdrawal. Dropouts will be replaced after consultation with the sponsor.

13.4 Ethics Committee

Before the commencement of the study, approval from the Bastyr University Institutional Review Board will be obtained. The principle investigator will provide ##### with documentation of ethical review board approval of the protocol and the informed consent document before the study may begin. The ethical review board will review the protocol as required. The principle investigator must also

provide##### with the ethical review board's approval of any revisions to the informed consent document or amendments to the protocol. This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki and the Belmont Report or the applicable guidelines on good clinical practice.

14. Final report

The draft final report will be by the principal investigator. This draft will be reviewed by the sponsor before a final report is prepared. The contents of the final report are, however, the responsibility of the investigators.

15. Publication

Relevant scientific results should, as a rule, be published. It is desirable that the investigators and the sponsor come to an agreement before any data are published. The sponsor has the right to use the results for purposes of registration or licensing. and has stipulated that study results be reported to Biocell Research, Inc with a three month delay thereafter before publication of results.

16. Time schedule

17. Budget See OSER application
Currently under moderate revision due to OSER recommendations.

18. Contract

19. Signatures

Scientist and Traditional Healers Meet in Abuja (Nigeria) on HIV/AIDS and Malaria

From Bioresources Development and Conservation Programme
Wednesday, November 1, 2000

SILVER SPRING, MD — The Nicon Nuga Hilton Hotel Abuja (Nigeria) will play host to leading scientists in drug development and traditional healers to explore ways of using herbal products for the treatment of malaria and AIDS, two of Africa's worst diseases. The International Conference on Traditional Medicine in HIV/AIDS and Malaria will be held December 5-7, 2000. The conference is organized by the International Centre for Ethnomedicine and Drug Discovery (InterCEDD) Nsukka Nigeria, an affiliate of the Bioresources Development and Conservation Programme (BDCP), Africa. The conference will address ways that research institutions and independent investigators in Africa, with reported positive clinical outcomes using traditional medical remedies, can improve their contributions to drug development or treatment of these diseases. The objectives of this unique event include: review of results of traditional intervention systems for the treatment of HIV/AIDS and Malaria; Identification of promising traditional remedies in current use; Provision of guidelines for the biochemical evaluation and standardization of traditional medicinal products and herbal remedies used for treatment; and Developing and harmonizing methods and protocols available for clinical outcome evaluation of safety and efficacy of traditional medical treatment of these diseases. The organization of the conference brings together several institutions and agencies in Africa, including BDCP, InterCEDD, the National Institute for Pharmaceutical Research and Development (NIPRID), Nigeria, National Agency for Food and Drugs Administration and Control (NAFDAC) Nigeria, Association for the Promotion of Traditional Medicine (PROMETRA), Senegal, African Scientific Co-operation on Phytomedicine and Aromatic Plants (ASCOPAP), Cameroon.

It is expected that drug development experts from Europe, America and Asia will join their counterparts in Africa to formulate methods for "fast tracking" the discoveries reported from various research laboratories into low cost medicines for the treatment of malaria and AIDS. According to Prof. Akubue, Director of InterCEDD, "This meeting is an important contribution to the global fight against malaria and AIDS because it brings together experts in pharmacology, medicinal chemistry and drug developments to review the work done so-far on the use of medicinal plants for the treatment of malaria and AIDS. We have very positive responses from several scientists, including those from the World Health Organization and national health authorities". One of the main organizers of the conference, BDCP, has a network of

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laboratories in eight counties throughout Africa. The main focus is drug development from the stage of discovery to commercialization, while ensuring that local communities and source countries derive maximum benefits for their biological resources and intellectual contributions. Capacity building and conservation of biological diversity underlie all of BDCP's activities. BDCP's international office is in Silver Spring, MD. InterCEDD conducts an integrated research program for drug development and commercialization of potentially useful products. InterCEDD provides a full service phytomedicine research facility that standardizes traditional remedies with clearly demonstrated safety and efficacy profiles.

For further information contact: www.bioresources.org or www.intercedd.com.

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