NUTRITION AND THE DEVELOPMENT, TREATMENT, AND PREVENTION OF HIV DISEASE IN WOMEN, INFANTS, AND CHILDREN

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National Institute of Child Health and Human Development (NICHD)
(http://www.nichd.nih.gov/)

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.865

THIS PA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS PA

The National Institute of Child Health and Human Development (NICHD) invites new and experienced basic scientists, epidemiologists, and clinical investigators to submit research grant applications to further understanding of the relationship between nutrition and HIV. Applications are encouraged that address preclinical or clinical, biomedical and/or behavioral research that concentrates on studies of: (1) nutritional factors and HIV transmission; (2) nutritional requirements for optimal growth, development, and maintenance of health; (3) impact of HIV infection on breastfeeding; (4) interactions between antiretroviral therapies, diet, nutrition and health; (5) nutritional assessment methodologies; and (6) specific functional biomarkers of outcome related to the nutrition/HIV relationship.

This announcement is intended to stimulate and strengthen a multidisciplinary approach to a complex, under-researched area and to form a basis for future research.

RESEARCH OBJECTIVES

Background

The interaction of HIV infection and AIDS with nutritional status has been a distinguishing characteristic of the disease course since the earliest days of the epidemic. In many areas of the developing world, particularly sub-Saharan Africa where HIV infection is endemic, concomitant malnutrition both in terms of macronutrient malnutrition, i.e., marasmus and kwashiorkor, and the "hidden hunger" of micronutrient deficiencies is also prevalent.

In the early days before the infectious agent was identified, AIDS was referred to as "slim disease" to reflect the characteristic wasting syndrome associated with the natural history of HIV/AIDS and related diseases. In reference to the nutrition and HIV relationship, most of the research attention has been focused on the impact of the disease on metabolism and, in particular, the AIDS wasting syndrome. Little attention has been paid to the potential role of nutrition in relation to the infectivity of the virus (nutrition-viral interaction), transmission of the virus (nutrition-host interaction), HIV pathogenesis and disease progression, resistance to opportunistic infections, or the efficacy of available interventions. Further, much of the evidence that does exist with regard to either the metabolic consequences of HIV infection or the potential role of diet or specific nutrients in the course of HIV infection is limited to data collected from adult patients. Although some data exist about the deleterious effect of HIV infection on the growth of infected children, little data exist about the role of nutrition in either mother-to-child transmission, subsequent sequelae of the disease or response to treatment in infants or children.

In assessing the diet/disease relationship, four general approaches are available: measurement of dietary intake, anthropometric assessment, assessment of biochemical indices of nutrient status, or direct nutritional intervention. The use of one of these approaches to the exclusion of the others to explore the nutrition and HIV relationship is problematic for the following reasons:

1. It is difficult to make any inferences about biochemical indices without knowing an individual's dietary intake.
2. Given the metabolic consequences of HIV disease and its treatment, e.g., the effect of antiretroviral (ARV) therapy on body composition, reliance on anthropometry in the absence of information about diet and/or nutritional biochemistry will result in potential invalid conclusions about HIV and nutrition per se.
3. Aberrant circulating levels of a particular nutrient may be due to inadequate intake or an inherent biochemical problem associated either directly with HIV infection or in response to HIV-related opportunistic infections (OI).
4. Without knowing the pre-supplementation status of an individual, it is difficult to distinguish between the elimination of dietary deficiency and the correction of an inherent nutritional anomaly associated with either HIV infection or concomitant OI.

5. It is necessary to use the appropriate biochemical or physiological biomarker to distinguish between these latter two contingencies, to avoid drawing invalid or inaccurate conclusions concerning the role of essential nutrients in HIV infection.

Research Scope

This PA encourages research using appropriate combinations of available nutritional assessment methodologies to address any of the issues listed below. The following are examples of topics that might be proposed for study in response to this announcement. However, these are only examples and are not meant to be limiting.

- Nutritional/dietary factors affecting maternal to child transmission of HIV infection;
- Nutrient requirements of HIV-infected infants and children for optimal growth, development, and maintenance of health;
- Impact of HIV infection on breastfeeding, to include changes in maternal nutritional requirements before and during lactation, changes in milk composition consequent to HIV infection, impact of suboptimal nutritional status on lactation in HIV-infected women, differences between children infected in utero or perinatally and those infected during breastfeeding in terms of health outcomes;
- Potential interactions among ARV therapies, diet, nutrition and health including: (a) Potential impact of nutritional status on efficacy of interventions including ARV in women and children; and (b) potential impact of ARV on nutritional status of HIV-infected women, infants, and children;
- Impact of sub-optimal nutritional status on health of HIV-infected women of reproductive age;
- Potential interactions among nutritional status, "traditional medicine," and/or ARV;
- Surveillance of at-risk populations: Part of the difficulty in extracting the role that nutrition might play in the course of HIV infection is that once the infection is established, it has its own metabolic consequences. Therefore, pre-infection data are needed in high-risk populations as well as comparative data by age and sex for demographically similar, uninfected children. Such data sets should include an appreciation of current dietary intake patterns utilizing available food composition data for indigenous foods.

Applications that include proposals for the development of nutritional assessment methodologies and specific functional biomarkers of outcome related to the nutrition/HIV relationship are encouraged, as are proposals that employ methods that could be effectively deployed in field settings in resource-poor environments.

MECHANISM OF SUPPORT

This PA will use the NIH Research Project Grant (R01) and Small Grant (R03) award mechanisms. As an applicant you will be solely responsible for planning, directing, and executing the proposed project.

For information on the new NIH Small Grant Research Program (PA-03-108) see http://grants.nih.gov/grants/guide/pa-files/PA-03-108.html.

The R01 should be used for full-scale research projects. The R03 mechanism is appropriate for small research projects that can be carried out in a short period of time with limited resources (total annual direct costs of up to $50,000 per year for up to two years). Examples of such projects include pilot or feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; or development of new research technology.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_I_1.htm.

ELIGIBLE INSTITUTIONS

You may submit an application if your institution has any of the following characteristics:

- For-profit or non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic or foreign
- Faith-based or community-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his/her institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

- Direct your questions about scientific/research issues to:

Jack Moye, Jr., MD
Pediatric, Adolescent and Maternal AIDS Branch
6100 Executive Boulevard, Room 4B11, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 496-7350
FAX: (301) 496-8678
Email: moyej@mail.nih.gov

- Direct your questions about financial or grants management matters to:

Mary Ellen Colvin
Grants Management Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, 8A17, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 496-5482
FAX: (301) 402-0915
Email: mc113b@nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS:

Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING $500,000 OR MORE PER YEAR:

Applications requesting $500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than $500,000 must carry out the following steps:

1) Contact the IC program staff at least six weeks before submitting the application, i.e., as ou are developing plans for the study;
2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,
3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

SENDING AN APPLICATION TO THE NIH:

Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING:

Applications must be mailed on or before the receipt dates described at http://grants.nih.gov/grants/funding/submissionschedule.htm.

The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight weeks.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with

the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate R01 applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- Receive a written critique
- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- Receive a second level review by the appropriate national advisory council or board.

REVIEW CRITERIA

The following criteria will be applied to both R01 and R03 applications.
However, the NIH R03 small grant is a mechanism for supporting discrete, well-defined projects that realistically can be expected to be completed in two years and that require limited levels of funding. Because the research plan is restricted to 10 pages, a small grant application will not have the same level of detail or extensive discussion found in an R01 application. Accordingly, reviewers should evaluate the conceptual framework and general approach to the problem, placing less emphasis on methodological details and certain indicators traditionally used in evaluating the scientific merit of R01 applications including supportive preliminary data. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or from investigator-generated data. Preliminary data are not required, particularly in applications proposing pilot or feasibility studies.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- Significance
- Approach
- Innovation
- Investigator
- Environment

The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the Principal Investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below.)

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below.)

ADDITIONAL CONSIDERATIONS

DATA SHARING: The adequacy of the proposed plan to share data.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance to program priorities

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION:

Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD:

Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH:

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III

clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS:

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent

statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES:

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS:

This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42

USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.