University of Maryland Baltimore and Affiliates Request to Conduct Studies with Human Subjects

Status: Approved
Initial Submit Date: 6/7/2007

Section A: GENERAL INFORMATION

Protocol Number: H-29314

A1. Protocol Title: IMPACT OF INFANT FEEDING PRACTICES AND AGE AT INITIATION OF ANTIRETROVIRAL TREATMENT ON GROWTH AND TREATMENT OUTCOMES AMONG HIV-INFECTED NIGERIAN CHILDREN LESS THAN 36 MONTHS OF AGE

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Economic Interest: No

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Economic Interest: No

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A5. Funding Sources:
NIH

A6a. Institutions where work will be performed:
Other Sites

A6b. Research will be conducted outside of the United States:
Facility/Institution: University of Benin Teaching Hospital and University of Abuja Teaching Hospital, Nigeria
Contact/Investigator: Dr. Austine Omoigberale and Dr. Adaora Okechukwu
If documentation of assurances has not been sent to the Office of Research, please explain:
For the University of Benin Teaching Hospital: IORG0001295, IRB00001722, Exp 21-Sep-08, FWA00001144, Exp 21-Sep-08
For the University of Abuja Teaching Hospital: IORG0005009, IRB00005988, Exp 2-Aug-10, FWA00011836, Exp 2-Aug-10

Section B: REVIEW PATH DETERMINATION
ORS will consider this protocol for Expedited review.

Is this an emergency situation? No

If this is a drug study, is an investigational new drug (IND) application required? N/A

If this is a device study, is an investigational device exemption (IDE) application required? N/A

If the research involves ONLY blood collection, are subjects healthy, non-pregnant adults whose weight is at least 110 pounds, with amount drawn less than 550 ml in an 8 week period, and with collection not occurring more frequently than 2 times per week? N/A

If the research involves ONLY blood collection for other adults and children, considering age, weight and health of subjects, is the amount drawn in an 8 week period less than 50ml or 3 ml per kg, and with collection not occurring more frequently than 2 times per week? N/A

Does the research involve ONLY the collection of biological specimens for research purposes by noninvasive means? (e.g. Hair; extracted teeth; excreta, sputum and external secretions; placenta removed at delivery; mucosal and skin cells collected by scraping or swab) N/A

Does the research involve ONLY the collection of data through noninvasive procedures (not involving general
anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves? (e.g. EKG, ECHO, EEG, Ultrasound, MRI)  Yes

Does the research involve ONLY materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis)?  N/A

Does the research involve ONLY the collection of data from voice, video, digital, or image recordings made for research purposes?  N/A

Does the research involve ONLY individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies?  Yes

Does the research involve pedigree studies, collection and/or storage of specimens for DNA analysis or gene transfer?  No

B2. Exempt From UMB IRB Review

Not Applicable

Section C: JUSTIFICATION

Malnutrition and growth failure are consequences of HIV infection in children and is characterized by poor linear and ponderal growth. It is well documented that there is impaired physical growth in children infected with HIV, and poor growth has been suggested to be an early indicator of disease progression in children. Poor growth is also associated with an increased risk of mortality.

Among African children, much needs to be learnt in the area of nutrition and pediatric HIV infection. It is well established that gut-associated CD4+ lymphocytes and other mucosal-associated cells are severely impacted during primary HIV infection which results in reduced absorption of nutrients. With antiretroviral therapy being introduced in these resource-poor settings where malnutrition is also widespread, there is a need to evaluate growth and change in nutritional status among children receiving antiretroviral treatment in this setting, taking into consideration important factors such as infant feeding practice which is critical for growth and age at initiation of treatment which is critical for antiretroviral treatment outcomes.

The overall objective of the WHO/UNAIDS/UNICEF guidelines on HIV and infant feeding is to increase child survival by promoting appropriate feeding practices for HIV-exposed infants and young children, and at the same time minimize HIV transmission through breastfeeding. Current WHO/UNAIDS/UNICEF guidelines for infant and young child feeding in the context of HIV states that "when replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS), avoidance of all breastfeeding is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life" and should be discontinued as soon as replacement feeding AFASS conditions are met. However, the issue of infant feeding in the context of HIV continues to be a dilemma in resource-poor settings because replacement feeding is not always an acceptable, feasible, affordable, sustainable or safe option and avoidance of breastfeeding is associated with risk of malnutrition and infections. Particularly there is little information on the benefits of breastfeeding to already infected infants, treated or untreated, in terms of growth and nutritional status.

Section D: PURPOSE

1. To characterize linear and ponderal growth over a 12-month period among HIV-infected Nigerian children (<36 months of age) receiving antiretroviral treatment and to evaluate the association between early infant feeding practice and linear and ponderal growth. Secondary aims will examine modifying effects of baseline nutritional status, age at initiation of antiretroviral treatment, stage of disease and baseline CD4% in the relationship between feeding modality and growth outcomes

2. To examine the association between early infant feeding practice and immunologic outcomes of antiretroviral therapy among HIV-infected Nigerian children (< 36 months of age) over a 12-month follow-up period
Section E: PROTOCOL RISK/SUBJECTS

E1. Risk Category

Minimal - That encountered in daily life or at a routine doctor's visit.

E2. Subjects

Gender: Both
Age: Child (1-12 yrs)
Ethnicity: ALL RACES INCLUDED
Primary Language: English, Local Dialect

Groups to be recruited will include: Patients

Vulnerable populations to be recruited as subjects: Children, Women of child-bearing potential

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

The biological mother of the child eligible to be recruited into the study will be asked for consent. Consent for participation will include information about the purpose of the study and why her child is being asked to join the study. She will also be asked if she would be willing to answer some questions about the feeding of her child. If she agrees and provides her consent, her child will be recruited into the study. No child will be enrolled without the biological mother's consent.

Section F: DESIGN/PROCEDURE

F1. Design

Select one category that most adequately describes your research: Questionnaire/survey/interview

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This multi-site study is a prospective cohort in design and will also include medical chart abstraction. Study subjects will be recruited both from among those just initiating treatment who will be prospectively followed for 12 months, and from among those who initiated treatment within the last 10 months whose data will be extracted from existing hospital records, and who also will be prospectively followed from the point of enrollment up to 12 months following initiation of treatment. For example, a child who has been on treatment for 6 months at the time of study recruitment will be followed for another 6 months.

Data collection will be both primary and secondary. Primary data collection will include the use of a questionnaire to collect information on infant feeding practice, and anthropometry (weight, height/recumbent length, mid upper arm circumference (MUAC), head circumference (HC)) taken at baseline (i.e. at initiation of treatment) and during routine follow-up clinic visits. With the exception of questionnaire on infant feeding practice, all data are collected and recorded under the routine standard of HIV care for children. Secondary data collection will involve abstraction from medical records previously collected data (where applicable) from initiation of treatment and from previous clinic visits and will include baseline characteristics such as age at treatment initiation, baseline CD4 count/CD4%, baseline clinical disease stage, weight, length/height, MUAC, HC at baseline and at every follow-up clinic visit, and CD4 count/CD4% taken every 3 months.

Inclusion criteria

1. Child HIV-infected based on positive HIV-1 DNA PCR below 18 months of age or positive HIV serology at age 18 months or greater
2. Age <36 months
3. Receiving antiretroviral treatment
4. Biological mother available for interview and agrees to participate
5. Biological mother is conversant in standard English, Hausa or Pidgin English

Exclusion criteria
Any inclusion criteria not met.

F2. Monitoring Plan

The PI will monitor the study and report study related adverse events to the IRB.

F3. Procedure

As part of the routine clinical examination during clinic visits, the child's weight, length/height, mid upper arm circumference and head circumference measurements will be taken. These measurements will be taken by trained hospital staff. Recumbent length will be measured in children <24 months in the supine position using an infant length measuring board/infantometer. Standing height will be measured in children <24 months old using a stadiometer. All measurements will be taken by trained hospital personnel as part of routine clinical examination and recorded to the nearest 0.1 cm. Mid upper arm circumference (MUAC) and head circumference (HC) measurements will be taken using a measuring/insertion tape and recorded to the nearest 0.1 cm. Weight measurements will be taken using a baby weighing scale with the child wearing light clothing. Older children will be weighed using an electronic scale. All measurements will be recorded to the nearest 0.1 kg. After all anthropometric measurements have been taken, the mother of the child will be interviewed about the feeding practices she adopted during the child's first six months of life, and up to the time of the study. This will be done using an interviewer-administered questionnaire. Prior to data collection, interviewers will be trained and the data collection instrument tested in pilot runs.

F4. Study Schedules

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<th>Study Schedule</th>
<th>Enrollment</th>
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Section G: SAMPLE SIZE/DATA ANALYSIS

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 0 Worldwide: 202

Provide rationale for choosing the sample size:

We plan to enroll at least 202 children in the proposed study. With an estimated loss to follow-up of 20%, we expect to have complete data for a sample of 161 children. This sample size was derived by considering a range of estimated differences in change in height-for-age z-score (ΔHAZ) and change in weight-for-age z-score (ΔWAZ) that can be detected between 2 feeding groups (mixed-fed vs exclusively breastfed/not mixed-fed) after 12 months of antiretroviral therapy. The calculations were made based on the assumptions of alpha = 0.05, power = 0.8 and n2/n1=0.37 (for unequal sample size between the two feeding groups using data from previously conducted pilot study). The sample size was estimated at 161 children (117 in the mixed-fed group, 44 in the exclusively breastfed/not mixed-fed group) based on a calculation designed to allow the detection of a difference of at least 0.25 z-scores in mean ΔHAZ and ΔWAZ with a standard deviation of 1.0 after 12 months of treatment between children who are mixed-fed and exclusively breastfed/not mixed fed.
G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Children will be categorized into feeding modalities based on how they were fed during the first 6 months of life. Feeding practice will be treated as a categorical variable defined as follows: exclusively breastfed (EBF); predominantly breastfed (PBF); replacement fed (RF); mixed fed (MF). We will also categorize children by age at treatment initiation as follows: treatment initiated <12 months of age vs treatment initiated after 12 months of age. We will compare growth and nutritional status outcomes (mean height-for-age, weight-for-age and weight-for-height z-scores) among children by infant feeding modality and by age at initiation of treatment. Growth in each exposure category will be compared to international growth reference curves. The z-scores represent the number of standard deviations above or below the median value for a reference population of that age. Height-for-age, weight-for-age and weight-for-height z-scores will be computed using the WHO Anthro 2005 software, which uses the international growth reference developed from the WHO multicenter growth reference study. A z-score of 0 corresponds to reference median, while a z-score of 1 indicates that the child's weight or height is 1 standard deviation above the median weight or height of the age- and gender-specific reference population. Children with height-for-age, weight-for-age and weight-for-height z-scores <-2 will be classified as stunted, underweight and wasted, respectively. Differences in mean z-scores between feeding groups will be tested using one way analysis of variance or simple regression. Proportions of those stunted, wasted and underweight in each exposure category will be compared using chi-square tests. Change in CD4 count/CD4% will also be compared by exposure category using analysis of variance. The generalized estimating equation (GEE) approach, which takes into account the correlation between repeated measurements on the same child, will be used to model longitudinal anthropometric data. Multivariate regression models will include covariates such as age at initiation of treatment, baseline nutritional status, stage of disease, CD4 count/%, and current age.

Section H: POTENTIAL RISKS/DISCOMFORTS

This study will involve no more than minimal risk to the child. No invasive methods are associated with this study. All anthropometric measurements will be taken by trained hospital staff during clinic visits as part of routine clinical examination during clinic visits and will present only minimal inconvenience to the child. The questions to be asked on interview are factual regarding infant feeding and not anticipating to be upsetting to participants. The time to complete the interview is estimated to be 15 minutes.

Section I: POTENTIAL BENEFITS

Describe potential benefits to be gained by the individual subject as a result of participating in the planned work.

All mothers/ caregivers will be given nutrition counseling to promote the health and well-being of the children.

Describe potential benefits to society of the planned work.

It is expected that this study will provide improved understanding of infant feeding in the context of HIV infection. Infant and young child feeding in HIV infection has continued to present a dilemma in resource-poor settings where replacement feeding is not an acceptable, feasible, affordable, sustainable or safe option. We expect that this study will afford us the opportunity to understand which infant feeding modality is most beneficial for HIV-infected children who are receiving treatment, an area in which there is little information. Findings from this study could have important policy implications regarding infant and young child feeding in the context of HIV care and treatment in resource poor settings.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

The benefits of participating in this study include receiving nutrition counseling which will help promote the health and well-being of the child. No invasive methods are associated with this study and anthropometric measurements taken is part of routine clinical examination during clinic visits and presents no more than minimal risk to the child. Thus, benefits outweigh risks.

Section J: CONSENT PROCEDURES
J1. Consent Procedures

Who will recruit subjects for this study?
- PI
- PI's staff

Describe consent procedures in detail.
Recruitment will be done in the hospital during the child’s regular clinic visit. For those who meet the inclusion criteria, the mother or caregiver will be approached, and the study will be described in detail. For those who are interested in participating in the study, informed consent will be carried out prior to enrollment of the child into the study. The informed consent will be conducted in English, Hausa or Pidgin English, which ever the mother or caregiver is fluent in. The vast majority of the population in the region speaks at least one of these languages, and the ability of the mother/caregiver to converse in one of these three languages is one of the inclusion criteria. Any potential subjects who appear not to understand the study in the judgment of the investigators will not be enrolled. If the individual is not able to read in English, Hausa or Pidgin English, then the consent will be read to them in the presence of a witness unconnected with the study team. Those agreeing to participate but not able to read in English or Hausa or Pidgin English will have the option of signing the Informed Consent document with their signature or thumbprint. The witness who participated in the informed consent process will also sign as witness on the informed consent document. A copy of the informed consent document will be given to all participants.

J2. Waiver of Consent

Will this research require a waiver of consent? No
Will this research require a privacy waiver (for entire study)? No
Will this research require a partial privacy waiver (for recruitment)? No

Explain why the research could not practicably be conducted without the waiver(s).

If waiver of informed consent requested, explain why the waiver will not adversely affect the rights and welfare of the subjects, and, if appropriate, describe plans for providing subjects with additional pertinent information after participation.

If privacy waiver requested, provide a brief description of the PHI for which use or access is necessary [including sources of the PHI].

If privacy waiver requested, provide a plan to protect the identifiers from improper use and disclosure and to destroy the identifiers at the earliest opportunity consistent with the conduct of the research (or provide a health or research justification for retaining the identifiers).

If partial waiver (for recruitment) is requested, describe how initial contact will be made. Briefly sketch introductory remarks.

Section K: CONFIDENTIALITY

Will research data be tied to individual subject’s names or medical record number? Yes
Will research data be coded? Yes

Where will research data with identifiers be kept? How will such data be secured?
The information with linkages of unique identifiers to study subjects will be kept under lock and key at the hospital sites. No records will be left on desks or in any public place at any time. Privacy of study subjects will be protected and confidentiality maintained at all times. Only de-identified information on study subjects will be used for data analysis.
Who will have access to research data with identifiers?

Only staff at the hospitals will have access to the information with linkages of unique identifiers to study subjects. The listed investigators at the University of Maryland and Johns Hopkins School of Public Health will only have access to the electronic version of the data which would be completely de-identified and unlinked.

Will you obtain a Certificate of Confidentiality for this study? No

Please further discuss any potential confidentiality issues related to this study.

All data collection will be conducted in private examination room setting. All data will be housed in password-protected computers with limited access by study investigators and staff.

Section L: COST/PAYMENT

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so, state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). Will the sponsor be responsible for costs of injury or illness related to the research? If no, explain who will be responsible.

Only one questionnaire will be administered beyond the standard of clinical care; hence, the risk of study related injury is very small. There is no compensation or payment available in the event of a study related injury.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar amount: 0

Distribution Plan:

Section M: EHS/GENETICS

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm that could result from participation in this research. In your discussion, consider the following aspects: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family’s pedigree will be presented or published, please describe how you will protect family member’s confidentiality?

Section N: SAMPLE COLLECTION

None

Section O: DRUG STUDIES

Is this study placebo-controlled? No

Placebo information:

List of all drugs to be used in this study:

Drug information:
Section P: DEVICE STUDIES

Device Category: N/A

IDE:

IDE Sponsor:

Regarding your device study, could potential harm to subjects be life-threatening? No

Regarding your device study, could potential harm to subjects result in permanent impairment of a body function? No

Regarding your device study, could potential harm to subjects result in permanent damage to a body structure? No

Section R: ADVERTISEMENTS

None