SUMMARY STATEMENT

PROGRAM CONTACT: [redacted]

(Privileged Communication)

Release Date: **12/12/2016**

Revised Date:

Application Number: **2 R01 AI098472-06**

Principal Investigator

GANDHI, MONICA

Applicant Organization: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Review Group: **BSCH**
Behavioral and Social Consequences of HIV/AIDS Study Section

Meeting Date: **11/15/2016**
Council: **JAN 2017**
Requested Start: **04/01/2017**

RFA/PA: **PA16-160**
PCC: **A23E**

Dual IC(s): **HD**

Project Title: **"Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables**

SRG Action: **Impact Score:** [redacted]

Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**

Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**

Animal Subjects: **10-No live vertebrate animals involved for competingappl.**

Gender: **1A-Both genders, scientifically acceptable**

Minority: **5A-Only foreign subjects, scientifically acceptable**

Children: **1A-Both Children and Adults, scientifically acceptable**

Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
6		
7		
8		
9		
10		
TOTAL	[redacted]	[redacted]

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

2R01AI098472-06 GANDHI, MONICA

RESUME AND SUMMARY OF DISCUSSION: This proposed renewal seeks to extend the results of the prior study which showed that small hair samples could be used to monitor exposure and adherence to ARVs in HIV-infected pregnant women, children, and adults. Now the team seeks to extend this method of monitoring adherence to oral PrEP and other long-acting methods of preventing HIV infection, such as long-acting injectables (cabotegravir) and the dapivirine vaginal ring. The proposed study will obtain hair and plasma samples from three other studies that are on-going in Arica. The Sustainable East Africa Research in Community Health (SEARCH) trial is providing PrEP to at-risk persons, the HIV Open-Label Prevention Extension study is assessing the dapivirine vaginal ring, and the Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial (A5359) in the AIDS Clinical Trials Group is examining long-acting injectables in HIV-infected patients. The goal of developing predictive biological adherence measures that work across both HIV+ and HIV- individuals and, moreover, that work with new ARV delivery methods give this innovative study the potential to have a substantial public health impact. The study team is very strong and they have been highly productive in the prior funding period. The proposed extension of the hair sampling methodology to the participants in three on-going studies will allow the team to extend significantly extend their adherence measurement work into the monitoring of the pharmacokinetics of PrEP, vaginal rings and long-acting injectables in populations at high risk for HIV. The committee's overall enthusiasm for the many strengths of this renewal application was very high.

DESCRIPTION (provided by applicant): Three lessons of the PrEP (pre-exposure prophylaxis) clinical trials - that adherence is critical to effectiveness, that pharmacologic adherence measures are more reliable than self-report, and that daily pill-taking is difficult –must be applied to the next phase of HIV prevention research. This phase will investigate oral PrEP roll-out and optimization in high incidence settings, as well as novel long-acting methods for preventing HIV infection, such as injectables or vaginal rings. The vaginal ring prevented HIV acquisition in two recent trials, but poor adherence to consistent ring insertion dampened overall effectiveness. Injectable PrEP with long-acting cabotegravir is of interest, but will require adequate drug levels to be effective, especially at the end of dosing intervals and with missed visits. Pharmacologic metrics integrate biology (pharmacokinetics, PK) and behavior (adherence) and will be crucial to interpreting effectiveness with real-world oral PrEP, rings and injectables. Our group has helped pioneer the use of small hair samples (which are easy to collect, store and ship) to monitor exposure (PK) and adherence to antiretrovirals (ARVs). During the first funding period of this R01, we made significant progress on our original aims, demonstrating that hair levels of ARVs, which monitor long-term exposure, are stronger predictors of treatment success than self-reported adherence (or plasma levels) in HIV-infected pregnant women, children, and adults. We have also shown preliminary utility of hair levels of tenofovir (TFV)/emtricitabine (FTC) to monitor adherence and toxicities with oral PrEP. This proposal will leverage three important trials to explore key knowledge gaps that will arise in the next phase of HIV prevention work: The Sustainable East Africa Research in Community Health (SEARCH) trial (Dr. Havlir, chair and co-I) has just launched a large study providing oral PrEP to at-risk individuals in 16 communities in Africa. The HIV Open-Label Prevention Extension (HOPE) study in the Microbicide Trials Network (MTN) (Dr. Baeten, chair and co-I) will assess open-label use of the dapivirine vaginal ring. The Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial (A5359, Dr. Castillo- Mancilla, co-chair and co-I)) in the AIDS Clinical Trials Group (ACTG) will examine long-acting injectables in HIV-infected patients with a history of poor adherence. All 3 trials will collect hair and plasma for drug levels, and track robust outcomes, to allow us to 1) investigate hair levels as metrics of adherence with the vaginal ring and oral PrEP in Africa and examine patterns of adherence (e.g. daily, around periods of risk, just prior to visits) by combining data in plasma and hair; and 2) examine hair levels as easy-to-collect metrics for PK monitoring with the use of injectables. The overarching goal of this renewal is to develop an integrated package of highly predictive biologic adherence and pharmacokinetic measures spanning PrEP

delivery methods and optimization strategies. Defining predictors and patterns of adherence to oral PrEP and rings, as well as metrics to monitor PK with injectables, will inform public health interventions in HIV prevention.

PUBLIC HEALTH RELEVANCE: Pre-exposure prophylaxis (PrEP) with oral tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) works, but measuring PrEP drug levels to assess adherence in the PrEP trials helped us understand that 1) drug levels measure adherence better than self-report; and 2) it is difficult to take a pill every day. New ways to prevent HIV will involve testing a vaginal ring that is inserted monthly or injections of a long-acting antiretroviral (like cabotegravir), but we must examine drug levels in the human body when studying these novel tools to truly understand how well they work. This study will look at drug levels in small hair samples in three important trials (studying oral PrEP in Africa; the dapivirine vaginal ring in Africa under real-world conditions; and injectable agents in the U.S.) to see if hair measures can monitor the effectiveness of HIV prevention delivered via exciting new modalities and in high-incidence settings.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact: This is a renewal application for a R01 from an accomplished group proposing additional studies of hair levels of ARV in both treatment and prevention studies. The first R01 yielded 20 papers, and most of the original aims were accomplished, with the exception of analysis in the PROMIS study (analyses are on-going). In the new proposal, Aim 1 will study TNF and FTC levels in persons in the SEARCH study on PrEP who convert and who do not convert, looking at the impact of drug levels on seroconversion and renal toxicity, as well as the predictors of adherence and patterns of adherence. Aim 2 will study women in MTN 025 who sero-converted and who did not while assigned to use the dapivirine vaginal ring. Aim 3 will study PLWH who are taking long-acting cabotegravir with LA rilpivirine in a phase 3 ACTG trial. The work is highly significant, has a strong scientific premise, and the methods are robust. There are minor issues; notably the methods of the patterns of adherence, which can yield novel information, are undeveloped, and the segmental analysis is underutilized and has not been accomplished in the Gandhi lab. These are easily addressable and do not diminish enthusiasm for the proposed work.

1. Significance:

Strengths

- “Objective” measures of adherence are needed, especially in prevention research where VL cannot be monitored.
- Aims will study hair levels in approved and experimental PrEP modalities (TNF/FTC, dapivirine vaginal ring, cabotegravir long-acting injection).
- Hair levels are ideally suited to study research participants from resource limited areas.
- Proposed work will include both hair and serum levels, allowing triangulation of data.

- Team has been very productive and is integrated into important HIV treatment and prevention trials and networks.
- Premise is sound and if successful the work will yield critical insights into adherence to PrEP in important contexts.

Weaknesses

- Aim 1, renal toxicity: how is this different than the paper in press in Lancet HIV?

2. Investigator(s):

Strengths

- Excellent set of investigators, including the necessary support from the parent studies.

Weaknesses

- None noted.

3. Innovation:

Strengths

- This method remains an innovative approach to studying cumulative drug exposure.
- Using hair levels to study next-generation PrEP in resource-limited areas is very innovative.

Weaknesses

- The segmental analysis is novel but only used in Aim 3; would it not yield useful information in the other Aims?

4. Approach:

Strengths

- Aim 1 (SEARCH PrEP study): rigorous sampling and data analysis plan; estimated 100 sero-converters who failed PrEP, and 300 non-converters randomly selected from the others on PrEP.
- Aim 2 (MTN 025): similar sampling and analysis plan of estimated 60 DPV ring converters and 180 DPV ring wearers who remained negative.
- Aim 3: (ACTG study A5359, LA cabotegravir with LA rilpivirine): adds segmental analysis of the hair segments to study PK of CAB over the dosing interval (one month).
- Has commitment from relevant PIs and study procedures already include collection of hair samples.
- Overall methods are robust.

Weaknesses

- Aim 1: renal toxicity: not clear what the proposed studies add to the “in press” study showing the utility of hair levels in predicting adherence.
- Aim 1 and 2: the patterns of adherence analyses are novel and in some ways the most unique opportunity in these Aims, but are least developed; methods of data analysis are not adequately described.
- Aim 3: RPV concentrations are not addressed.

- It does not appear that the segmental analyses of hair samples has been successfully piloted in the Gandhi lab.

5. Environment:

Strengths

- Excellent environment at UCSF, including required laboratory equipment.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- The proposal adds procedures to studies being conducted and monitored by other groups, and the additional procedure of hair sampling is safe. However, the human subjects plan does not address data confidentiality. Presumably the PI will get identifiable data that must be protected.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically.
- Race/Ethnicity: Distribution justified scientifically.
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable.
- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically.
- Small numbers of children 15-17 may enroll in the parent studies; mix of men and women and African and US cohorts. Of note, all Hispanics from the ACTG study are planned to be mixed race, which seems unlikely.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Renewal:

- This PI has been productive during the first period of support, with 20 papers and completion of most of the aims; one is on-going due to delay in starting the parent protocol.

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

- Not clear what data a student at UW, working with Dr. Baeten, would have to work with or what responsibilities he or she would have; justification for this cost is weak.

CRITIQUE 2:

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 2

Overall Impact: This is a proposal for a renewal of a highly successful R01 examining how hair samples could be used to measure ART adherence within several of the NIH-funded clinical trials networks studies. With the renewal application, the investigators propose to use hair measures to investigate innovative long-acting methods for preventing HIV infection, such as the dapivirine vaginal ring and long-acting injectables. This renewal would continue collaborations with the networks (e.g. MTN and ACTG) and forge a new collaboration with a large study examining novel mechanisms to deliver oral PrEP on a population level in Africa (SEARCH.) The prior R01 was highly successful in terms of generating papers (20+) and establishing the use of hair sampling to measure adherence in both treatment and prevention trials. The renewal has strong potential to advance critical work related to adherence measurement within these trials, while simultaneously developing novel strategies for adherence measurement and pharmacokinetics monitoring.

1. Significance:

Strengths

- Adherence has consistently shown to be vital to the effectiveness of both HIV prevention and treatment options.
- Measuring adherence via methods that move beyond self-report is more reliable and valid. Hair samples have been shown in the prior R01 to be more reliable for this purpose.
- Optimizing PrEP roll-out in resource-limited settings and exploring long-acting prevention methods are two critical avenues in which rigorous development and clinical trials are needed. The need to measure adherence accurately goes hand in hand with these research needs.
- Adherence and need for long-acting options are the two keys to “PrEP 2.0” strategies and this proposal would address both.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Extremely strong group of investigators who pioneered the work in this field and remain the experts.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Coupling hair measures with plasma metrics and with other shorter-term measures will allow for a better sense of patterns of behavior and for how pharmacokinetics parameters may impact these strategies.
- Assessing novel methods of prevention: vaginal rings, long-acting injectables.
- Hair measures remain a fairly novel way to assess adherence.

Weaknesses

- Extension of prior work. Hair measures well-established though seldom implemented at scale.

4. Approach:

Strengths

- In this renewal, would extend the use of hair samples for the following network studies: 1) To evaluate concentrations of PrEP drugs in hair and plasma as biomarkers of adherence and predictors of effectiveness in a large community cluster randomized trial (SEARCH) at multiple sites in sub-Saharan Africa. 2) To investigate the use of hair levels as a long-term measure of dapivirine exposure in the openlabel trial of the dapivirine vaginal ring (MTN-025). And 3) to examine the utility of hair levels for PK monitoring of LA cabotegravir in a diverse population (A5359).
- Novel additions for #2 include looking at hair levels in comparison to self-reported adherence, plasma and residual ring dapivirine and for #3 include examine correlations between CAB levels in hair and plasma at the end of dosing intervals.
- Leverages existing clinical trials and networks to better provide adherence insight.
- Plan to use random sampling of the small fraction of non-seroconverters is more cost efficient and feasible than testing specimens from all participants.
- Additional aim to look at association of hair levels with renal toxicity, which extends work from adherence/efficacy monitoring into monitoring for adverse events.

Weaknesses

- Hair sampling continues to have weaknesses in its ability to detect behavioral patterns related to adherence. Pairing with additional biological and other markers of adherence is a helpful addition, as is the strategy towards developing a package of adherence monitoring strategies.
- Questions about feasibility of use in certain cultural contexts remain.

5. Environment:

Strengths

- Excellent combination of potential trial environments.
- Settings with clinical research methods and controls already in place because of funded network trials.
- UCSF and Hair Analytical Laboratory very well-equipped to carry out these investigations.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- No issues identified

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- DSMP in place for the trials in which these evaluations will be embedded.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically.
- Race/Ethnicity: Distribution justified scientifically.
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable.
- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically.
- Appropriate inclusions, following the inclusion and exclusion criteria of the parent trials.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Renewal:

- Highly productive prior R01, with excellent progress report and publication record. Compelling arguments for extending the hair measure evaluations within these new trials to answer additional, important questions.

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 2
Investigator(s): 1
Innovation: 3
Approach: 2
Environment: 1

Overall Impact: This application is an R01 renewal application which aims to incorporate hair analyses to examine adherence to PreP with oral medications, vaginal rings, and long-acting injectable antiretroviral medications. Hair analyses will be incorporated into three ongoing international studies in Africa. There are numerous strengths to this application. The investigators were very successful and productive in the first 5 years of the R01, in which they published 20 manuscripts. The application extends the R01 which used hair to examine adherence to HIV treatment with ARVs among women and children, and now proposes to use hair to examine adherence to PrEP and new cutting edge ARV delivery (vagina rings and long-acting injectable ARVs). The study leverages existing resources by being integrated into three existing large studies in Africa. The team of investigators is outstanding, and it is clear from the structure of the research team and letters of support that integration of the proposed project into the existing studies will be feasible and successful. The approach is clear and justified; analyses are appropriate and thoughtful.

1. Significance:

Strengths

- Examining adherence using hair samples will provide important information that is above and beyond the information that can obtained from blood samples and self-reported data.
- The reach of the proposed project is ambitious and feasible given the existing infrastructure and prior history of success.
- The premise of examining adherence to PrEP in real-world settings with the use of new technologies (vaginal ring and long-acting injectable ARVs) is strong, important, and significant.

Weaknesses

- Similar type of research has been conducted by this team, but has focused on HIV treatment rather than PrEP, making this proposal a small incremental step forward.

2. Investigator(s):

Strengths

- The team of investigators is outstanding. The team consists of those involved in all parts of the proposed project.
- Dr. Gandhi has successfully worked in similar situations with international large ongoing studies previously, and has demonstrated success.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Using hair to examine adherence for PrEP and cutting edge ARV delivery systems is innovative.

Weaknesses

- Using hair to examine adherence itself is not so innovative.

4. Approach:

Strengths

- The proposed study will be well integrated into 3 ongoing large studies in Africa, which is an efficient use of resources.
- The study design is elegant in that hair samples will be collected from all participants, but only those with seroconversion, along with a random sample of control participants will be analyzed (using 3:1 sampling of control:seroconversion).
- The analytic strategies are thoughtful, and will examine various correlations. Much will be learned from the analytic techniques.
- Aim 3 will include segmental analyses of hair markers.
- Overall, the approach is robust, will get a lot of “bang for the buck”.
- The inclusion of studies that focus on vaginal rings and long-acting injectables is a strength.

Weaknesses

- The power analyses include relatively large effect sizes to achieve a substantial level of power. However, the power analyses calculations appear to be conservative in that they do not account for repeated measures. Thus, a smaller effect size is likely to be achieved.

5. Environment:

Strengths

- The environment is outstanding. The numerous letters of support clearly demonstrate the feasibility of incorporating the proposed project into the existing studies.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically.

- Race/Ethnicity: Distribution justified scientifically.
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable.
- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Renewal:

- In the prior period of R01 funding, the investigators where very successful in disseminating findings--20 manuscripts were published.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 2 R01 AI098472-06; PI Name: Gandhi, Monica

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by

averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.