CFAR Supplement Announcement in HIV/AIDS – FY2019

The CFAR Program at the National Institutes of Health (NIH) invites applications from currently funded CFARs that are eligible for administrative supplements. CFARs in the last year of their funding cycle, a bridge period, or NCE are NOT eligible to apply. **Each CFAR can submit a maximum of four supplement applications for topics 1-5. CFARs can submit one application to the TB topics.**

Purpose and Scientific Areas of Interest

The purpose of this administrative supplement opportunity is to **support innovative research projects, inter-CFAR meetings, and shared instrumentation** that address key gaps in HIV/AIDS and will advance the field. This opportunity should build research capacity and be consistent with the recent NIH HIV/AIDS research priorities (NOT-OD-15-137).

Topics 1 and 2 must be responsive to the overall Ending the HIV Epidemic (EtHE): A Plan for America initiative which is focused on four key pillars (Diagnose, Treat, Protect, and Respond). For additional information and background on the EtHE initiative, please refer to the special CFAR/ARC supplement announcement emailed to the CFAR list previously.

1. **Promoting Viral Suppression in Health Disparity Populations Engaged in HIV Care in Rural Communities**

The purpose of this supplement opportunity is to foster collaborations between CFAR investigators and rural public health entities focused on capacity building and pilot research projects to address gaps in the HIV care continuum. For decades, there has been concern about health disparities in rural communities, and these disparities are evident for HIV/AIDS prevention and treatment. Among individuals engaged in care, racial/ethnic minority, substance using, less educated, and lower income populations are less likely to be prescribed ART, achieve viral suppression on ART, and maintain sustained viral suppression.

Nonurban residence has also been associated with lower likelihood of HIV testing and later HIV diagnosis in multiple US settings and populations, and there is evidence that there are unique barriers to retention in care and viral suppression in these communities. Access to public health services including HIV, HCV, or STD testing and treatment may be limited. Stigma and confidentiality in small communities pose additional challenges to establishing and maintaining those services. Many rural communities have experienced dramatic increases in prescription drug use that have led to increases in injection drug use, opioid overdose, and incidence of acute HCV, as well as potential for localized HIV and HCV outbreaks. State-level public health surveillance systems often have difficulty detecting infectious disease outbreaks in rural areas.

An important component of this opportunity is collaboration between the scientific and service entities in communities, to optimize the match of proposed research directions with local needs. The collaboration could be with local public health department and/or non-governmental organizations which focus efforts on the HIV care continuum. Rural public health infrastructure varies from community to community. A useful resource: the National Association of County and City Health Officials (NACCHO) report, 2016 National Profile of Local Health Departments, describes local

health department governance, infrastructure, funding, leadership, workforce, programs, practice, and more.

The following is a HRSA-supported website that provides links for criteria that defines rural communities: https://www.ruralhealthinfo.org/am-i-rural/help. Projects that are based in Micropolitan Statistical Areas of 250,000 persons or less as defined by the U.S. Office of Management and Budget will be considered responsive. Applicants should propose collaborations in the 7 states (Alabama, Arkansas, Kentucky, Mississippi, Missouri, Oklahoma and South Carolina) recently identified as having a substantial rural burden.

Applicants should describe: a timeline of activities for a process of collaboration with the public health partner, a needs assessment if necessary, and a potential pilot research project which could address one of the following HIV care continuum topics, with attention to health disparity populations engaged in HIV care in rural communities, as relevant (including but not limited to):

- Studies of pathways into, through, and/or out of care, to better understand the multi-level factors that influence this process, and to identify critical junctures for intervention
- Pilot intervention studies for rapid and effective linkage of individuals diagnosed with HIV to primary medical care and interventions designed to optimize re-engagement and retention in HIV care, with particular attention to intervention modalities (e.g., mobile technologies) that address the unique barriers in rural communities
- Pilot studies to measure the impact of community health workers and community-based programs to improve viral suppression and self-management among PLWH prescribed ARTs at rural clinics
- Exploratory/planning studies to identify potential synergies between existing local resources i.e., community-based programs and workers, rural clinics, financial, housing and other social programs and telehealth/mobile or outreach connections to urban centers; gather feasibility pilot data, and plan multi-year intervention to address gaps in HIV care continuum
- Studies of care integration and service co-location, and other forms of differentiated care, to advance better outcomes in the HIV care continuum, including less conventional and underutilized settings and providers (e.g., dental clinics, pharmacies)
- Studies of provider, clinic and/or systems-level factors that may influence the adoption, uptake and sustainability of evidence-based interventions in rural community and clinical settings
- Pilot studies to identify strategies to promote ART initiation and adherence in PLWHs from health disparity populations engaged in care in rural settings, and to simultaneously reduce high risk behaviors

Supplement awards are for one year with maximum funding per application of up to **$150,000** Direct Costs, not including third party indirect costs.

2. **HIV Healthcare Systems and Differentiated Care Approaches to Improve Viral Suppression**

This supplement topic is intended to support pilot research to test approaches in healthcare delivery systems (e.g., structural, policy, provider, practice) that aim to reduce gaps in the HIV care continuum and improve viral suppression in key populations. Among potential differentiated care approaches, applicants are encouraged to consider the use and effectiveness of existing local and regional community-based programs employing community health workers (CHW) to support durable HIV suppression, engagement and retention in HIV care. To be responsive to the EtHE initiative,

applicants must partner with HRSA, CDC or IHS supported community-based organizations (CBOs) or community health centers (CHCs) within the 50 jurisdictions as well as the 7 states with substantial rural burden. To have the greatest impact applicants are encouraged to collaborate with CBOs/CHCs that have a large service area.

Responsive studies could include, but are not limited to:

(Please note clinical trials are not allowed but clinical studies are permissible)

- Studies to pilot and evaluate the use of electronic health "dashboards" and quality improvement approaches to monitor and improve care continuum gaps at various levels (e.g., clinic, municipal, state)
- Studies to evaluate the impact of novel ART prescription and refill strategies such as electronic prescribing, synchronized refill intervals, and mail-based delivery on viral suppression
- Studies addressing the impact of innovative prescription packaging on population-level rates of ART medication refills and viral suppression
- Studies to evaluate whether finance-informed interventions (e.g., reduced medication co-pays) can improve population-level rates of ART medication refills and viral suppression
- Studies investigating how variations in the HIV care team composition can improve rates of viral suppression at the clinic level
- Mixed-method studies of CHW practices and roles (e.g., case management, medication adherence support) including how they interact with PLWH clients and their support network, the broader community and clinic services staff (social workers, nurses) to improve health outcomes; and studies of mechanisms by which CHW are able to initiate and maintain effective therapeutic relationships with PLWH (e.g., how and why these relationships produce good outcomes)
- Develop and pilot modifications to current HIV-focused CHW approaches to improve linkage of complex patients to HIV care including those with substance use and/or psychiatric disorders
- Pilot or evaluate strategies that make use of existing systems of community lay health workers such as peer recovery support workers in the substance use system to improve viral suppression in populations characterized by poor or variable ART adherence

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3. **Elucidating Metabolic Consequences of PrEP and ART**

The changing landscape of HIV treatment and prevention as well as the long-term exposure to multiple medications present unmet challenges to elucidate and clarify the ensuing effects that are known to impact physiological pathways in diverse organ systems. Emerging information suggests that acute actions may differ from those observed after persistent exposure to these drugs. The broad range of ages and ethnicities affecting people prone to be exposed to HIV further obscures our understanding of these processes. In addition, the presence of other diseases impacts the way these medications are metabolized and the presence of commonly occurring conditions like cardiovascular disease, hypertension, liver disease, obesity and diabetes that are commonly treated with multiple drugs lead to intricate interactions that may impact and change the natural history of these diseases and HIV progression. The goal of this topic is to gain mechanistic insight into the interactions between PrEP, ART, and/or HIV-associated inflammation and these medications. This knowledge may provide a basis for individualized therapy. There is an interest in the gaining a mechanistic insight into these interactions in the young exposed to ARV in utero, young adults, women of reproductive age and pregnant women.

Supplement requests addressing one or more of the following topics will be of greatest interest:

- Comparative studies characterizing early versus late metabolic changes after implementation of PrEP or ART therapies
- Projects addressing the acute metabolic effects of additional or novel ART therapies imposed on previous HIV medical management
- Trends in virologic or immunologic status in subjects with chronic conditions including obesity, diabetes, hypertension, CVD, pulmonary complications such as COPD and pulmonary hypertension, anemia, inflammatory bowel disease, plaque psoriasis, NASH, and renal insufficiency after initiation of HIV therapies or PrEP
- Pharmacokinetic and pharmacodynamic changes of commonly used medications to treat obesity, diabetes, hypertension, CVD, pulmonary complications such as COPD and pulmonary hypertension, NASH, anemia, or renal failure after the implementation of PrEP in subjects at risk or ART in those infected with HIV
- Identification of sex-specific risk factors that increase the likelihood of developing metabolic comorbidities after and during PrEP or ART therapies
- Interactions of exogenous cross-sex hormonal therapy used by transgender individuals with PrEP or ART contributing to the development or metabolic comorbidities

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4. **Obesogenic Mechanisms During HIV Infection**

Emerging data suggest that obesity is a critical factor in the pathogenesis of HIV non-infectious comorbidities; such as metabolic syndrome, diabetes, and cardiovascular disease. Conserved intracellular pathways link the biology of T cell metabolism, the immune response, and diabetes. Emerging information indicates that obesity is both a consequence and a cause of the immune activation, which is associated with these non-infectious comorbidities in people living with HIV. Mounting evidence indicates the importance of gastrointestinal barrier dysfunction and microbial translocation as a cause for this chronic immune activation and inflammation. Fat is likewise an immunologically active tissue. HIV viral products affect adipocyte differentiation, which may be independent of plasma viremia. In addition, ART also induces fat accumulation. These effects may pre-dispose individuals to the development of obesity and alter expression of pro-inflammatory cytokines that might predispose people living with HIV to morbidity and mortality. This supplement topic invites projects that interrogate the biological basis of the emerging problem of obesity in the HIV-infected population. Elucidation of these underlying mechanisms is requisite for the development of therapeutic and preventive strategies. Inclusion of women of reproductive age, pregnant women adolescents and children in these studies is of interest. Studies of changes in microbiome and virome in these populations is also of interest.

Responsive studies could include, but are not limited to:

- Effect of HIV-induced gastrointestinal changes on the enteric microbiome and products of bacterial metabolism, intestinal inflammation, intestinal barrier dysfunction, and/or adipocyte biology
- HIV viral interactions with adipocytes
- Interactions of antiretroviral agents with adipocytes
- Polypharmacy effects of drugs to treat HIV comorbidities, coinfections, and comorbidities in addition to ART on adipocytes
- HIV-specific changes in fat biology and metabolism
- Consequences of HIV-specific changes in fat tissue on T cell and tissue macrophage function
- Impact of obesity on the development of noninfectious comorbidities such as the metabolic syndrome, diabetes, pulmonary disease (e.g. COPD), NASH, obstructive sleep apnea, or cardiovascular disease in people living with HIV

- Identification of mechanisms underlying sex differences in HIV-associated obesity

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5. Innovative Technologies for Basic Research on HIV and Comorbidities

Research technologies continue to advance at a rapid rate. Often there are barriers that prevent early career investigators from gaining access to cutting edge technologies because their research is at a nascent stage and they lack the funding to acquire or implement new technologies. They may also lack the resources to incentivize productive collaborations with investigators in complementary disciplines that have access to advanced technologies and the expertise to capitalize on them.

The purpose of this supplement topic is to enable early career investigators to integrate cutting edge technologies and relevant new collaborations into well-defined basic research pilot studies that will provide the basis for future research grant applications. Applicants are encouraged to think critically about how their research could be facilitated by newly emerging technologies, and what new scientific hypotheses or directions could be explored by applying new research tools or collaborations. Research should focus on key basic science gaps within the investigator's area of interest.

Examples of new and emerging technologies to consider include, but are not limited to:

- **Data Science Innovations**
  - Quantitative and analytic approaches, processes, and systems to extract knowledge and insights from large and complex ("Big Data") data sets including but not limited to clinical, virology, molecular, genomics, behavioral, observational, pharmaceutical, community, geospatial, and even social media data. Scientific questions are at the discretion of the of the applicant but may involve mining social or phylogenetic networks, economic data, claims data, patterns of incarceration, substance use, clinical or behavioral implementation science or outcomes data.
  - Artificial intelligence, machine learning, and/or deep learning, including analyses of existing clinical imaging data
  - Bioinformatics and computational biology
- **State-of-the-Art Omics Studies**
  - Single-cell analyses, including laser-capture microdissection of tissues
  - Mass cytometry
  - CRISPR-mediated genetic knock-out or engineering
- **Bioengineering and Nanotechnology**
  - Microphysiological systems or tissue chips
  - Synthetic biology
- **Cellular and Molecular Imaging**
  - Super resolution fluorescence microscopy
  - Cryo-electron microscopy
  - Single molecule imaging
- **Force Spectroscopy**
  - Atomic force microscopy
  - Optical tweezers
- **Multi-modal Imaging**
  - Multiplexed ion beam imaging (MIBI)
  - Focused ion beam / scanning electron microscopy (FIB/SEM)
  - Correlated light and electron microscopy (CLEM)
- **Other Combinations of Orthogonal or Multi-modal Technologies**

Supplement awards are for one year with maximum funding per application. To accommodate the higher expense of some technologies, awards can be up to **$200,000** Direct Costs for one year, except for topics under Data Science Innovations, which will be capped at **$100,000** Direct Costs for one year, not including third party indirect costs.

6. **Tuberculosis Research (supported by Division of Microbiology and Infectious Diseases (DMID), NIAID –TB mono-infection studies allowed)**

TB is the leading infectious disease killer world-wide and TB co-infection remains the leading cause of mortality among those infected with HIV. Major gaps in our understanding of this disease interfere with the ability to address this important public health crisis. In September 2018, NIAID published the "NIAID Strategic Plan for Tuberculosis Research" that proposes efforts to better understand the immunology and pathogenesis of TB and to develop new tools to more effectively combat the disease. In support of the Strategic Plan, supplement requests could include, but are not limited to the following areas:

Improving the fundamental knowledge of TB

- Identification or validation of host or bacterial factors that lead to control of disease or progression to active TB
- Analysis of mycobacterial virulence factors or mediators related to immune evasion and host-pathogen dynamics
- Characterization of mycobacterial metabolic states and their interaction with the host immune system and/or treatment efficacy

Improving the diagnosis of TB

- Discovery or validation of new biomarkers that predict the risk of progression to TB disease, treatment outcomes or risk of relapse, or improved characterization of drug resistance
- Discovery or validation of biomarkers that lead to improved diagnosis of TB in pediatric populations
- Development or validation of point-of-care diagnostics to distinguish latent TB from active disease or to provide rapid drug susceptibility testing

Developing tools and resources to advance research in understanding, preventing, diagnosing and treating TB

- Evaluation or improvement of animal models representative of human disease for TB drug, drug regimen or vaccine evaluation
- Development of critical reagents to improve the ability to conduct studies in TB animal models
- Evaluation of sampling tools and biomarkers that enable tracking the presence, growth and distribution of mycobacteria in humans or animal models following infection and throughout disease progression
- Development or validation of in silico models to predict optimal drug combinations for treatment of TB and predict synergies or antagonistic activity between agents

Supplement awards are for one year with maximum funding per application of up to **$150,000** Direct Costs, not including third party indirect costs.

Eligibility

Project leaders for all scientific areas of interest are restricted to early career investigators who have never received an R-series, R01-equivalent or U-series research grants. Established investigators in non-HIV fields who have never received an NIH research award for HIV/AIDS studies are also eligible (except for the TB topic). Post-doctoral fellows are eligible to apply if they will assume a faculty position by the time the supplement project and funding begins. Established investigators can be the project leaders for the core equipment and inter-CFAR meeting topics.

Studies that are a continuation of previously funded CFAR supplements or funded NIH applications that do not address new specific aims are not eligible for funding under this announcement. Additionally, a proposed supplement application that is linked to a proposed application not yet funded is not eligible for funding under this announcement.

Application Instructions

Requests submitted in response to this opportunity must use the PHS 398 forms (rev. 1/2018) and include the elements in the request packet as described below. Applicants must submit each application as an e-mail attachment, in one file, in PDF format; however, the signature of the institutional official must be clearly visible. Font size restrictions apply as designated within the PHS 398 instructions

1) **Cover Letter** – Citing this Supplement Announcement, a request for an Administrative Supplement, and the following information:

- CFAR Principal Investigator and Supplement Project Director names
- Parent grant number and title
- Scientific area of interest for this supplement request
- Amount of the requested supplement
- Name and title of the authorized institutional official
- Phone, email, and address information for the PI, the PD and the institutional official

The cover letter must be signed by the authorized organizational representative/institutional official.

2) **PHS 398 Form Page 1** (Face page) (MS Word PDF) – Provide requested information as follows:

- The title of the project (Box 1) should be the title of the parent award and a descriptive title of the supplement application.
- The scientific area of interest should be cited under title in Box 2, and the “yes” box should be checked.
- Enter name of CFAR PI and the name of the project director. (Example: Dr. Bill Jones (CFAR PI) and Dr. John Smith (Project Director).
- The remaining items on the face page should be filled out in accordance with the PHS 398 application instructions.

3) **PHS 398 Form page 2**

Note: The project “summary” is that of the administrative supplement, not the parent grant. All other information requested on Form Page 2 should be provided.

4) A **brief proposal** describing the request (with parts 4a and 4b **not exceeding five pages** in total), should include:

a. An introduction that clearly states the **scope of the overall request,** the anticipated contribution of the requested supplement, and how the project addresses the NIH HIV/AIDS Research Priorities (NOT-15-137).

b. The **research project plan** should include the background and rationale for the proposed application; a description of the activities to be undertaken, and roles of key staff; expected outcome of these activities; expected follow-up plan upon completion of the supplement; a description of how the supplement and follow-up plan are expected to achieve this outcome ("value-added"); and plans to monitor and evaluate the ability of the activities to achieve the outcome. Most importantly, applicants must clearly indicate how the proposed activities outlined in the supplement requests are expected to lead to development of the stated goals. Mentorship and collaborations must be explained.

c. **Budget** for the supplement with a justification that details the items requested, including Facilities and Administrative costs and a justification for all personnel and their role(s) in this project. Note the budget should be **appropriate for the work proposed** in the supplement request. If funding for travel to a scientific meeting is included, it must be for the early stage investigator and must be for the purpose of presenting data from this supplement award.

   A statement regarding the expenditure of currently available unobligated grant funds of the parent CFAR grant will be required. The CFAR must include a description of the plans to spend remaining funds in order to demonstrate the need for additional funds.

d. **Biographical Sketch** for all new Senior/Key Personnel and for mentors. Use the new biosketch format in MS Word. Please note the personal statement should be related to the CFAR supplement project.

e. **Human Subjects/Vertebrate Animal documentation** (if applicable). Include a current Human Subjects/Institutional Review Board (IRB) or Vertebrate Animals/Institutional Animal Care and Use Committee (IACUC) approval date, if applicable. If proposing a study involving vertebrate animals, the CFAR parent grant must already have vertebrate animal approvals in place. Otherwise, this information will be required at time of funding. All appropriate IRB and IACUC approvals must be in place prior to the initiation of a project. NOTE: Studies involving clinical trials are not allowed.

f. Further NIH-initiated administrative actions and approvals are required for ALL international studies (NOTE: this also includes the CFAR International Checklist requirement) and any clinical studies deemed above minimal risk or involving vulnerable populations.

g. **PHS 398 Checklist Form** MS Word PDF

   i. TYPE OF APPLICATION. Check REVISION box and enter your CFAR grant number;

   ii. Applicants must state that all federal citations for PHS grants will be met (e.g., human subjects, animal welfare, data sharing, etc.)

h. NO other support. This information will be required for all applications that will be funded. NIH will request complete and up to date "other support" information at an appropriate time after review.

i. NO resource page (unless there are new resources that will be used for this request)

j. NO appendices

k. Submit a letter(s) of collaboration endorsing the proposed request from all substantial participants. For topics 1 and 2 focused on EtHE, a letter of support must be provided from the collaborating partners (e.g. health departments or CBOs).

l. If applicable, please include letters of support for projects requiring access to data, samples, tissues, cutting edge technologies or etc. Include evidence to support the feasibility of enrollment, including descriptions of prior experiences and yield from research efforts employing similar referral sources and/or strategies for projects involving recruitment of participants.

m. For transitioning post-doctoral fellows, please include a letter from your institution confirming the transition to a faculty position that includes the start date.

Budget and Funding Information

Funding for supplements will be supported by the CFAR NIH co-funding Institutes. Funding for the TB research topic will be provided by DMID. The maximum funding allowed per application is described within each topic above. Funding for administrative supplements to existing CFAR grants will be available for up to one year in FY2019. Supplemental funds for these supplements will be provided to the Developmental Core of the CFARs.

How to Apply

This is a one-time announcement. CFAR staff will work with OSR submit the application to the NIH for you. Do not send applications to the NIH Center for Scientific Review.

Review Considerations

Upon receipt, applications will be reviewed by the CFAR Program Officers for completeness and responsiveness. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to this announcement, the application will be returned without review.

Applications that are complete and responsive to the announcement will be evaluated for scientific and technical merit, and alignment with the NIH AIDS research priorities by an internal NIH review group convened by the NIAID in accordance with standard NIH review procedures.

Review Criteria

The following criteria apply to all scientific applications, unless noted. Reviewers will also examine the appropriateness of the budget, in consideration of the research environment and the supplement request.

1. Evidence that the proposed project will enhance new multidisciplinary collaborations and exert a sustained, powerful influence on HIV/AIDS (or TB for topic 8) research;
2. Extent to which the supplement will address scientific gaps and/or development of new strategies which include a variety of scientific disciplines;
3. Adequacy that the strategy, methodology, and analyses are well reasoned and appropriate to accomplish the specific aims;
4. Utilization of existing resources (including CFAR Cores) and/or development of unique and appropriate expertise, technology, and resources at the CFAR institution(s) and other sites, as appropriate;

5. Degree of innovation in project selection and experimental design;
6. Quality and appropriateness of mentorship and collaboration for the research project;
7. Choice of appropriate project PI and co-investigators (e.g., scientific qualifications, commitment, and experience), as well as the collaborations with other institutions, if applicable;
8. Appropriateness of the budget, in consideration of the research environment, for the scientific projects and cores;
9. Feasibility to complete the project within the FY19 project period (e.g., this will range between 8-12 months depending on the parent CFAR grant).

Allowable Costs

Funding may be requested for any category normally funded by a CFAR grant that is required to fulfill the goals of the proposed request and must be fully justified.

Schedule for Applications

Review Date: ***6/21/19***

Earliest Anticipated Award (Start) Date: ***7/01/19***

Terms of Award

A formal notification in the form of a Notice of Award (NoA) will be provided to the grantee organization. The NoA signed by the grants management officer is the authorizing document. Once all administrative and programmatic issues have been resolved, the NoA will be generated via email notification from the awarding component to the grantee business official.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Reporting

Awarded administrative supplements will be required to submit a progress report to be included in the annual progress report of the parent grant. Progress reports should include a summary of the supplement projects and outcomes.

Award Criteria

The following will be considered in making awards:

- Relevance to NIH HIV/AIDS research priorities, or relevance to TB research priorities for TB research (topic 8)
- Relevance to EtHE priorities for topics 1 and 2
- Scientific and technical merit of the proposed project as determined by NIH convened internal review panel;
- Funding availability and;
- Program balance.