For a video that walks you through this template, and for other grant writing training, visit **http://tinyurl.com/7lluvex**

Instructions:

The goal of this template is to help you focus your aims, one vital component of writing a successful proposal. This template is derived directly from R01's of mine that were funded with scores better than the 5th percentile, and it has also been used by various people I've helped, several of whom have used it to score in the top few percentile. Bottom line is, when you combine this with some of the other aspects of a great grant (e.g. great team, great project, etc), this approach works.

The aims are a crucial part of winning over the reviewer. Your whole proposal should be written for a general science audience, not for just specialists in your field. This is particularly important in the specific aims. If you use specialized terminology without explaining it here, you will loose your reviewer's good will quickly, and your chances of funding are slim to none.

Keep it general, and keep it interesting. Make sure to cover each of the four key components: Why, Who, What, and How (Those are explained in my book, [Four Steps To Funding](#)).

And the most important thing: you must be proposing great work that your field cares about. If you're not proposing work that people care about, then great writing will not make any difference at all.

I want to thank Dr. Marshall Edgell for his initial inspiration for this template, and Dr. Peter Drain for his recent input to improve it.

Specific Aims

In the template below, I use examples from a proposal of mine that was funded with a very good score.

1. *1-2 sentences: Set the big picture, central challenge of your field that lots of people are interested in solving. For example: "Post-translational modifications (PTMs) on proteins can significantly affect their function and their interactions with other proteins, so a major component of mass spectrometry (MS) based proteomic research is focused on identifying post-translational modifications present in different cellular states." This should be the backdrop for the "Why" (for a complete explanation see [Four Steps To Funding](#)).*

2. *2-3 sentences: elaborate on the problem, and what has been going on in your field to solving it. This is the introduction to the "What," i.e. the theory behind what you're trying to do. But keep it interesting and for a general audience! Do not get bogged*

down in heavy factual details here, or your reviewer will become lost and uninterested. For example: "PTM analysis usually proceeds by one of two methods: bottom-up is the most common, whereby all proteins are digested into peptides and then individual peptides are analyzed by tandem mass spectrometry to find mass-shifts associated with the presence of modification(s). The second route is top-down analysis, where the mass of intact proteins is measured on a high accuracy MS instrument, and from the mass, protein modifications can be inferred due to a shift compared to the predicted mass in a protein database.*"*

3. *1-2 sentences: Name a general bottleneck in your field that is slowing or stopping progress towards achieving the big picture named in the first sentence.* **This is a critical part of your aims***! You must have a single, clear Gap that needs solving [clearing], in order to have a good proposal. This is your framing device for your "Why". For example: "Both methods have limitations - with bottom-up, it is difficult to find and analyze all the peptides associated with each protein, so there are usually gaps in coverage. Top-down is limited because a single mass measurement can be assigned to multiple isobaric (equal mass) combinations of modifications, so is not definitive."*

4. *1-3 sentences: elaborate on the Gap, making it more* **specific** *and* **focused***. For example: "*To overcome these limitations, several groups including our own have combined top-down with bottom-up (TDBU) analyses of post-translational modifications in proteins, using top- down data to predict possible modification scenarios, and bottom-up data to determine which scenario is correct. At present, there is no openly available software for automatically combining these two different types of data sets, and analysis by hand is extremely slow and time consuming.*"

5. *(optional) 1-2 sentences: Discuss the theory that leads up to your proposed solution, in general and non-technical terminology. Do not get bogged down in minute technical details here. (For the example I'm using here, no additional theory was presented, but many successful proposals present a bit of theory at this point, often as a prelude to a hypothesis).*

6. *1-2 sentences: Propose an approach to solving the roadblock. If you are working in a hypothesis-driven area of work, this is where you'll state your hypothesis. If you can tie this in with the "Who" your proposal will be stronger. From the Four Steps To Funding model, this is your "What" - i.e. your model of how the world works (within the area of your proposal). For example: "We are ideally positioned to build and deliver open source software to address these limitations, having extensive experience in both top-down and bottom-up software development, as well as experience in applying TDBU data to an exhaustive analysis of E. coli ribosomal proteins." In this example, we are proposing new software, and we are*

*also talking about our experience in building that software in the very same sentence. If this were a hypothesis, you'd do essentially the same thing, proposing your hypothesis and immediately showing why **you and your team** have the experience to be working on it.*

7. *(optional) 1-2 sentences: Explain why you and your team are the right people to implement this solution/approach. **This is another critical section, it is the Who.** You need to point out why not just anyone can do this work, and why you are qualified and ready to jump in and solve it. The best thing is to cite one or more previous papers of yours on the subject, or point to unpublished work, for example: "Our established development track record includes PROCLAME for top-down analysis (PROtein CLeavage And Modification Engine)[1] and GFS for bottom-up (Genome-based peptide Fingerprint Scanning)[2-4]."*

8. *1 sentence: "We are proposing to accomplish goal [or test this hypothesis] with the following specific aims:"*

9. *The aims are your How. They need to be credible, meaning that it is realistic that you can accomplish them given your skills, your budget, and your timeframe. Each aim needs not only a how, but also a Why, as in "why do this aim? What is its purpose for being?" The following structure is a great way to force yourself to answer not only the How but also the Why for each aim. You may be tempted to skip this. Do so at your own peril! This formula is proven to work. "Aim #: To X we will Y." - I've used this exact format on the last 5 funded proposals for ALL of my aims. It forces you to clearly state WHY you will do the aim (X) and HOW you will do it (Y). Sometimes the HOW (Y) is divided into several sub-steps, as a numbered/lettered list, and can even be more than one sentence, if absolutely necessary. For example: "Aim 1: To improve the identification of post-translational modifications and amino acid substitutions on proteins by combining top-down and bottom-up mass spectrometry data, we will **enhance our PROCLAME software to use a Markov chain Monte Carlo algorithm that can incorporate: a) intact-mass mass data from top-down analysis, b) peptide data from bottom-up analysis, and c) context-sensitive rules that use but are not limited by knowledge of where modifications are likely to occur. We will further enhance the program's assessment of modification frequency by ongoing analyses of protein databases like UniProt[5].**" Here, I have underlined the Why and **boldfaced** the How. Again, for a good aim, it must have both.*

10. *(optional)1-4 sentences: How clearing the hurdle fits into the big picture. For the NIH, this big picture needs to be tied to improving health or curing disease. For the NSF, this may be solving one of their named grand challenges. The more*

For a video that walks you through this template, and for other grant writing training, visit **http://tinyurl.com/7lluvex**

> *people afflicted and the deadlier the disease, the easier it is to establish the importance of the project in the big picture context. Now, in some proposals I've left this off and it hasn't hurt me, such as the one we've been using for an example. But here's an example. But here's an example from another well-scored proposal:* "By performing a differential analysis of proteins encoded by transcripts in a variety of tissue types, we expect to uncover knowledge about the location and timing of protein translation in cells, information about which transcripts get translated, and information about how many of the putative alternative exons predicted actually encode proteins. By enhancing genome annotation with these data, and by making the project data openly accessible to other researchers, we expect these data sets will become a rich source of information for those studying regulation and mis-regulation of the path from transcription to translation in disease conditions."

Comment on the Gestalt of this template from Peter Drain at U. Pittsburgh:

Grant writing is getting the money. Science is what you do when you get the money. Two distinct activities. First, get the money. Second, decide on the best science to do with that money. Getting funded and the science done with the funds are not the same. The bottom line is that grant writing is a learned skill with some key components that are not scientific but rather based on relating the study to the reviewers goal, in a word, relationships.

2. Specific Aims

Chronic fatigue syndrome (CFS) is a relatively common, often disabling disorder characterized by profound fatigue lasting at least 6 months, and other symptoms such as headache, poor sleep, myalgias, cognitive dysfunction, post-exertional malaise, and tender glands [1]. CFS is thought to be part of a spectrum of overlapping central sensitivity syndromes [2-4] that might share a common pathophysiologic mechanism [5]. Some suggest that central sensitization is influenced by afferent input from peripheral nerves, and that such input may play a key role in determining the threshold of central sensitivity and symptom expression in irritable bowel syndrome (IBS) [6], fibromyalgia (FM) [7], and possibly in other syndromes such as CFS.

We have observed that many with CFS have **neuromuscular dysfunctions** - specifically, restrictions in the physiologic range of motion of the limbs and spine. Our preliminary observations also suggest that applying a neuromuscular strain during the physical exam (via, for example, a passive straight leg raise) can amplify CFS symptoms.

Individuals with CFS and related central sensitivity syndromes can also manifest exaggerated sympathovagal balance (e.g., diminished heart rate variability: HRV) and impaired neural cardiac regulation (e.g., orthostatic intolerance [8, 9]). However, the association of resting neuromuscular dysfunction with sympathovagal balance is unknown. Moreover, the effect of exposure to an additional neuromuscular strain on CFS symptoms, sympathovagal balance, and central sensitization has not been examined. Our ***long-term goal*** is to understand the role of neuromuscular dysfunction in CFS and its interplay with autonomic and central sensitization. **Herein, we propose to evaluate whether individuals with CFS differ from controls with regard to neuromuscular function, and whether applying a neuromuscular strain amplifies CFS symptoms, sympathovagal balance, and central sensitization.** Thus, our Specific Aims are:

<u>Specific Aim 1</u>: To determine whether people with CFS show resting alterations in neuromuscular function, sympathovagal balance, and central sensitivity relative to matched controls.

We hypothesize that CFS participants will show neuromuscular dysfunctions (restricted range of motion on limbs and spine), exaggerated sympathovagal balance (diminished HRV), and greater central sensitivity (temporal summation) compared to controls.

<u>Specific Aim 2</u>: To determine whether a neuromuscular strain manipulation (NMSM) elicits immediate and delayed (next-day) increases in fatigue, sympathovagal balance, and central sensitivity, and reduces neurocognitive performance.

Using a NMSM versus a sham manipulation, we hypothesize that CFS participants exposed to the NMSM will immediately report greater fatigue, heightened central sensitivity, and poorer neurocognitive performance compared to CFS participants exposed to the sham manipulation and to controls exposed to either the NMSM or sham.

We also hypothesize that when assessed 24 hours later CFS participants who were exposed to the NMSM will continue to report greater fatigue, heightened central sensitivity, and poorer neurocognitive performance than CFS participants exposed to the sham manipulation and controls exposed to either the NMSM or sham.

Accomplishing these specific aims will allow us to determine whether neuromuscular dysfunction represents a peripheral marker that contributes to the pathogenesis of CFS symptoms and to heightened central sensitization.

SPECIFIC AIMS

The proposed research directly _meets the goals of the RFA-MH-12-061 – Promoting Engagement in Care and Timely Antiretroviral Initiation Following HIV Diagnosis (R34)_), which aims at reducing health disparities and testing interventions that impact adherence to HIV therapeutic regimens and retention in medical care.

HIV-infected women have demonstrated poor engagement and retention in care, which are expected to be due, in part, to co-morbid depression. Women consistently show higher non-adherence to antiretroviral therapy (ART) and lower retention in care rates compared to men and consequently higher mortality rates. [4,5] (+Rumptz MH, 2007) Furthermore, HIV-infected women are particularly vulnerable to suffer from depression compared to their male peers (19), with 69% of HIV-infected women evidencing prolonged symptoms of depression (18) compared to only 45% of men (Wisniewski, AB, 2005). In the context of HIV disease, it is well known that depressive disorders are one of the strongest predictors of suboptimal adherence to ART and retention in care. If left untreated, HIV-infected patients with depressive symptoms are less likely to respond to interventions designed to link patients to care (Gardner LI, 2009). Therefore, intervention strategies that simultaneously reduce depressive symptoms and improve adherence and retention to clinical care among HIV-infected women are urgently needed [6-17] (+Giordano and Gardner LI, 2009 + J. Simoni). While the proportion of minority women infected with HIV in the United States (US), particularly in the Southeast, is increasing significantly, little is known about effective intervention strategies and modes of intervention delivery that address HIV-infected women's barriers to retention and adherence to care (Ref.). Given that HIV-infected women are more likely to live in rural areas of the US where access to diverse healthcare services are limited, intervention strategies addressing retention to and adherence care will have to use non-traditional modes of health care delivery. Telemedicine distributed interventions can help to overcome structural barriers to retention and adherence to care while providing expert delivered specialty care.

Our _long-term goal_ is to develop an effective intervention that significantly improves clinical outcomes in HIV-infected women by decreasing depression morbidity and simultaneously increasing adherence to ART and retention in care. The _objective of this application_ is to culturally adapt an established and effective **c**ognitive-**b**ehavioral **t**herapy (**CBT-AD**) for depression and **ad**herence and test its feasibility and acceptability to HIV care adherence among HIV-infected minority women living in the rural South of the US (Safren, Gonzalez, & Soroudi, 2008). CBT-AD is based on the demonstrated association between depressive symptoms and poor ART adherence, and targets specific symptoms of depression that are seen as significantly interfering with an individual's ability to adhere to HIV care. Safren and colleagues (Co-investigator) previously have demonstrated the efficacy of CBT-AD in an urban primarily male patient population, while this proposal seeks to adapt this efficacious intervention in a rural, female population. [23]

In the proposed study, we will adapt the CBT-AD intervention to HIV-infected women in Alabama, a state with a significantly higher proportion of HIV-infected minority women than the national average (Ref.). We will use telemedicine technology to increase distribution of the intervention across rural populations in Alabama. Telemedicine has been successfully used in the delivery of mental health services - particularly in rural areas where mental health providers are scarce (Hilty 2006 & 2007, De Las Cuevas 2006). The intervention will provide general skills training in coping and problem solving with depressive symptoms and adherence to ART and will be modified to address retention in care.

To accomplish our main objective above, we propose the following **specific aims:**

1) **To evaluate the cultural relevance of CBT-AD by conducting formative research among HIV-infected women and HIV care providers to inform the cultural adaptation of CBT-AD intervention for HIV-infected women in rural areas of Alabama;**

2) **To systematically adapt the CBT-AD intervention to HIV-infected women residing in rural Alabama and telemedicine technology, using an iterative open-label – non-randomized process.**

3) **To assess the feasibility, acceptibility and preliminary behavioral efficacy of the adapted CBT intervention to address depression among HIV-infected women and retention and adherence to care by implementing a pilot randomized controlled trial (RCT).**

With respect to _expected outcomes_ the work proposed in specific aims 1-3 is expected to significantly contribute to our understanding of factors impacting depression treatment as well as retention and adherence to care interventions among HIV-infected women, in particular in underserved, rural areas that are increasingly impacted by the HIV epidemic. Such results will _positively impact_ the development of an R01 scale RCT, testing the efficacy and cost-effectiveness of CBT-AD among women across various HIV care settings, as will be detailed in the next section.

2. Specific Aims

In response to **PA-12-179: Exploratory/Developmental Clinical Research Grants in Obesity,** we propose a pilot randomized-controlled trial to evaluate the feasibility and effects of the non-deceptive (open-label) administration of placebo pills on objective (weight, physical activity) and subjective (quality of life, psychological well-being) outcomes in obese adults seeking weight loss.

Although the placebo effect is well-established [1-5], using placebos in clinical practice is considered unethical because deception ("intentional ignorance") is thought necessary to elicit positive responses. However, two recent open-label placebo studies— where patients were told they were receiving placebo pills—significantly reduced symptoms both in adults with Irritable Bowel Syndrome (IBS) and depression scores in adults with Major Depressive Disorder (MDD) [6, 7]. **These non-deceptive placebo clinical studies, which involved a single intervention visit, applied the perspective that placebo effects are not merely the result of ingesting an inert pill but also the effects embedded within the patient–clinician encounter; including a persuasive rationale for benefit, attention, ritual, and the modulation of expectations and perceptions.** While these studies indicate that open-label placebos can influence subjective (patient-reported) outcomes, it is unknown whether they can also influence objective (e.g., weight) and behavioral outcomes (e.g., physical activity, dietary intake).

> *"Developments in research on placebos suggest that the time has come to translate the science of placebo effects and knowledge regarding techniques for promoting placebo responses into clinical practice and medical education."* **Brody & Miller: Lessons from Recent Research about the Placebo Effect - From Art to Science. JAMA 2011; 306: 2612-2613.**

Obesity is a major public health problem and current behavioral treatments, even very intensive ones, often produce modest and short-lived weight loss [e.g., 8-11]. Thus, identifying alternative approaches that enhance obesity treatment outcomes is desirable. We will examine the feasibility and effects of open-label placebos **(OLP)** for obese adults seeking weight loss. **Specifically, we will conduct a pilot trial to evaluate whether, in obese adults given the identical self-directed weight loss program, the open-label administration of placebo pills—in the context of the patient-clinician relationship of education, reassurance, and positive expectation—produces greater weight loss compared to those who do not receive placebo pills (NO OLP).**

Specific Aim 1: Examine the feasibility of OLP for treating obesity.
Hypothesis 1a: OLP will be perceived by the majority of obese adults screened as credible and acceptable.
Hypothesis 1b: Those randomized to OLP will adhere >80% to the placebo pills "prescription."

Specific Aim 2: Evaluate whether OLP reduces weight.
Hypothesis 2: The OLP group will show greater weight reduction compared to NO OLP.

Specific Aim 3: Evaluate whether OLP has beneficial effects on behavioral (i.e., physical activity, dietary intake) and psychosocial (i.e., weight-related quality of life, well-being) outcomes.
Hypothesis 3: The OLP group will show greater benefits on these outcomes compared to NO OLP.

Sixty obese adults will be randomized to either: (1) OLP (where participants will be told that *"placebo pills made of an inert substance, like sugar pills, have been shown in studies to produce significant improvements in many people by activating mind-body healing and self-management processes"),* or (2) NO OLP. Prior to randomization, participants will be given the identical self-directed weight loss program and take part in a placebo orientation meeting. Within the context of a natural "give and take" interaction with a weight loss specialist, this meeting will provide the rationale for positive expectations that placebo treatment may increase their ability to lose weight. All participants will have the same quantity and quality of interaction with providers. Those randomized to OLP will take two placebo pills twice a day (adherence will be measured by Medication Events Monitoring Systems (MEMS) caps) over the course of the 12-week study, while those randomized to NO OLP will not. Change in body weight will be the primary outcome. Secondary outcomes will be physical activity (measured by accelerometer), dietary intake, psychological well-being, and weight-related quality of life. We will also assess the perceived effectiveness and global satisfaction with OLP.

This pilot trial will provide information on the feasibility of OLP for obesity, as well as on study design, retention, effect sizes, and outcomes assessment. Our long-term goals are to determine whether OLPs are beneficial for treating obesity, and, if so, to identify: (1) participant characteristics associated with positive response, (2) the mechanisms by which OLP operates, and (3) the best methods of administering OLPs to maximally harness its effects.

II. Specific Aims

In order to eliminate new pediatric HIV infections, save maternal lives, and simplify antiretroviral therapy (ART) implementation, current WHO guidance emphasizes triple ART for all pregnant and breastfeeding women regardless of CD4 count or clinical stage, called Option B.[1] The guidelines further recommend lifelong ART for these women in countries with generalized epidemics (Option B+). This recommendation provides the opportunity to achieve prevention of mother-to-child transmission (PMTCT) of HIV, treatment of HIV-infected pregnant women for their own health, and reduction of new HIV infections in sero-discordant couples.[2]

Despite the promise of Option B+ to remove logistical barriers—such as the need to obtain CD4 counts prior to prescribing ART for pregnant women—and to promote maternal health through life-long ART, this strategy brings challenges. Early reports from Malawi indicate 20-30% loss-to-follow-up in the first 3-6 months after ART initiation for pregnant and lactating women.[3-6] Additionally, a meta-analysis of 51 studies, many in sub-Saharan Africa, found that only 73.5% of pregnant women achieved adequate (>80%) ART adherence, with the proportion of postpartum women with adequate adherence being only 53%.[7] Evidence-based strategies to promote adherence to ART and retention of mother-baby pairs in HIV care during pregnancy, breastfeeding, and beyond are urgently needed in order to achieve the potential benefits of Option B+.

Barriers to PMTCT adherence and retention in care occur at the individual, interpersonal, community, and health facility levels.[8] On the individual level, women may lack information and motivation; while on the interpersonal and community levels, a woman may fear negative reactions, HIV-related stigma, and discrimination. At the health facility level, low quality services, including health care workers who hold negative views about women living with HIV and/or who do not recognize and help women to overcome social barriers to adherence, may contribute to high drop-out rates from PMTCT programs.[9-11] However, there is limited knowledge of specific facilitators and barriers to uptake and retention in care for Option B+.

We propose to gain understanding of and address potential barriers at three levels and rigorously test two evidence-based interventions that alone or in combination are likely to maximize ART adherence and retention in care among HIV-infected pregnant women and HIV-exposed infants in rural Kenya, using a cluster randomized 2x2 factorial design. The evidence-based interventions to be tested will include 1) community-based mentor mothers (MM) who will support HIV-positive women in the community and 2) individually tailored, theory-based mobile phone text messages to help retain women, and infants in HIV care. There is evidence that both of these interventions enhance uptake and retention in PMTCT and HIV services in sub-Saharan Africa,[12,13 14-17] but they have not been investigated in the context of Option B+.

The proposed study will be conducted in rural Nyanza Province, Kenya at 20 low-resource primary health care facilities and associated communities supported by Family AIDS Care and Education Services (FACES), a PEPFAR-funded HIV prevention, care, and treatment program. We will assess both process and outcome indicators using a 2x2 factorial design, in which equal numbers of clusters will be randomized to one of the interventions, both interventions, or standard of care. The interventions will be added to fully integrated high-quality HIV and antenatal, maternal, neonatal, and child health (ANC/MNCH) services already offered at these sites. **Our overall goal is to determine which intervention (or combination of interventions) maximizes ART adherence and retention in care in the context of Option B+ and thus improves maternal and infant health outcomes.** This goal will be achieved through the following specific aims:

> **Aim 1:** To evaluate the acceptability of lifelong triple ARV therapy given to HIV-infected pregnant women both for their own health and for PMTCT (Option B+), as well as facilitators, barriers, and acceptability of potential interventions for ART adherence and retention in care, using qualitative research methods.

> **Aim 2:** To compare service utilization outcomes (pregnant women's adherence to ART, women's retention in HIV care, and uptake of early infant diagnosis) in four study conditions (community MM intervention only, text message intervention only, both interventions, and control) using a 2X2 factorial design.

> **Aim 3:** To examine effects of the individual and combined interventions on maternal and infant health outcomes, including maternal CD4 counts/viral loads, and MTCT at 6 weeks, 12 months, and 18 months.

There is an urgent need to evaluate service models that maximize ART adherence and retention in care among women and infants in order for Option B+ to achieve its full potential. This study will support the scale-up of Option B+ in Kenya by identifying effective interventions and combinations of interventions that can reduce barriers and increase facilitators of optimal ART adherence and retention in care with the aims of reaching the elimination of mother to child transmission of HIV and significantly improving maternal health.

2. Specific Aims

We propose to evaluate the safety and feasibility of resistance exercise (RE) on body composition in children with Juvenile Idiopathic Arthritis (JIA). Determining whether RE is safe, well-tolerated and whether it improves the outcome of arthritis is explicitly stated as one of the research areas of clinical and public health need and interest for **Program Announcement 10-282: Pilot and Feasibility Clinical Research Grants in Arthritis and Musculoskeletal and Skin Diseases**.

> *"Achieving and maintaining normal body composition will be a key end point for optimal treatment of patients with JIA."* **Bechtold & Roth (2009), Natural History of Growth and Body Composition in Juvenile Idiopathic Arthritis**
>
> *"There is great potential for weight-bearing exercise to help combat the musculoskeletal changes of JIA."* **Long & Rouster-Stevens (2010), The role of exercise therapy in the management of juvenile idiopathic arthritis**

JIA is the most common chronic inflammatory autoimmune disease in children and a significant cause of childhood and long-term disability (1). Its prevalence ranges from 16 to 150 per 100,000 (1, 2), and symptoms include joint pain and tenderness, fatigue, and loss of range of motion. As a consequence of the disease, physical inactivity, and the medications used to treat JIA, these children often have reduced muscle mass and strength, and bone cross-sectional area and bone mineral density [BMD]. Although the newer disease modifying antirheumatic drugs (DMARDs) may minimize long-term sequelae of JIA, these patients still tend to experience considerable muscle and bone loss which may predispose them to experience health problems and accelerated functional decline in later years (3-6).

The American College of Rheumatology (ACR) recommends exercise for patients with arthritis. A recent Cochrane Review (7) of exercise in JIA shows that there have only been 3 randomized-controlled trials, all of which involved aerobic exercise only. Though improvements in functional ability, quality of life, and aerobic capacity all favored aerobic exercise, none were statistically significant compared to controls. **Moreover, these studies did not investigate the effects of the exercise on body composition and muscle strength, the primary outcomes in our proposed study, or symptoms or disease activity, the secondary outcomes in this study.**

Resistance exercise (RE) has been shown to be safe and well-tolerated in adults with rheumatoid arthritis (RA) and idiopathic inflammatory myopathies (e.g., dermatomyositis). Moreover, RE improves strength, reduces disease activity and impairment, and in some cases, reduces inflammation (e.g., 8-13). However, RE has not been rigorously studied in JIA. Because children with JIA suffer musculoskeletal disturbances driven by inflammation, we hypothesize that they would derive similar benefits from RE to those obtained in adults with inflammatory rheumatic diseases. **Thus, we will conduct a** randomized-controlled pilot study **to evaluate** the safety, feasibility, and effects of 12-weeks of RE **in children with polyarticular JIA.** The trial will be conducted in our exercise facility where the participants will be individually supervised and adherence will be closely monitored and documented.

Specific Aim 1: To investigate the safety and feasibility and effects of RE on the following primary outcomes: body composition, muscle strength, flexibility, and range of motion.

We will test the primary hypothesis that those randomized to RE will have significantly greater improvement in body composition (i.e., fat-free mass [FFM]), muscle strength, flexibility, and range of motion compared to those randomized to the control condition.

Specific Aim 2: To investigate the effects of RE on the following secondary outcomes: disease activity, aerobic capacity, inflammatory markers, pain, fatigue, functional ability, and quality of life.

We will examine if RE produces greater improvements in these outcomes compared to controls. Because of the absence of previous studies on these outcomes with RE, effects sizes are unknown. As an alternative to hypothesis testing, we will determine 95% confidence intervals in response to the interventions that will provide evidence worthy of further investigation in children with JIA.

This novel "proof of principle" pilot study will be the first randomized-controlled trial to evaluate the safety, feasibility, and effects of RE in children with polyarticular JIA. This innovative study should provide preliminary insights into the mechanisms by which RE might modify body composition, muscle strength, symptoms, and disease activity. The data will also provide preliminary data to inform an RO1 grant.

SPECIFIC AIMS

Adherence to HIV treatment recommendations—including adherence to both antiretroviral therapy (ART) and HIV care visits—is essential for persons living with HIV (PLHIV) to achieve health, longevity, and an undetectable viral load. Yet, only 20-25% of PLHIV in the United States (US) are virally suppressed.[1] Even among PLHIV who are followed regularly in interval cohort studies, ART adherence varies and is inadequate, *especially* in certain disadvantaged sub-groups, including women.[2,3] *There is evidence that HIV-infected women may have worse adherence to ART than men*,[3] and higher morbidity and mortality.[4,5] Women of color are at particularly high risk of acquiring HIV,[6] and have worse health outcomes once infected compared to White women.[7] Southern states in the US have the highest rates of new infections, particularly among Black, female, and poor populations, and the highest HIV case-fatality rates in the country.[8-10] There is an urgent need to identify barriers to engagement in care and to ART adherence among women living with HIV, particularly among minority women from diverse geographic regions of the country, in order to understand existing health disparities and develop responsive interventions.

One potentially important barrier to adherence to HIV treatment recommendations is HIV-related stigma. Studies suggest that stigma and discrimination not only threaten quality of life for PLHIV, but also impede ART adherence and *engagement in care*. Specifically, research has found that persons who perceive high levels of HIV-related stigma have lower acceptance of HIV testing,[11] lower access to medical care,[12] poorer ART adherence,[13] and lower utilization of HIV care.[14] However, there is need for further studies to determine the magnitude of these effects longitudinally, *to identify environmental factors that may underlie geographic differences in these associations*, and to elucidate temporal relationships to provide further evidence for causality. There are also limited longitudinal data on links between HIV stigma and immunologic and virologic outcomes—key consequences of poor adherence to HIV treatment recommendations. Furthermore, there are notable gaps in the literature on the roles of specific dimensions of stigma, as well as the interpersonal, psychological, mental health, and biological mechanisms that may explain the observed relationships.[15] There are also indications that stigma may directly affect health through pathways other than treatment adherence–via chronic activation of stress-responsive biological systems.[16] Finally, only a few studies have examined the intersection of HIV-related stigma with other forms of stigma and discrimination due to race, gender, socio-economic status, and other factors, which may exacerbate the effects of HIV-related stigma.[17,18] While these issues are particularly salient for minority women in the US, there are limited data examining the roles of HIV-related stigma and other *intersecting stigmas* in adherence and clinical outcomes for this population.

To address these gaps in knowledge, we will leverage the resources of the national Women's Interagency HIV Study (WIHS), which has been collecting data on HIV-infected women's treatment adherence, mental health, and immunologic and virologic outcomes for 20 years. In 2013, WIHS added new sites from the Southern US in response to shifts in the HIV epidemic. We have recently collaborated to add brief measures of internalized stigma and serostatus disclosure to national WIHS data collection, and the proposed study will enable us to *fund the continuation of those measures* in order to establish longitudinal effects (n=2100). We also propose a yearly supplementary visit at 3 WIHS sites (n=500) representing different parts of the country—California (San Francisco), the Deep South (Alabama/Mississippi), and the Southeast (Georgia)—to collect additional measures of theoretically important dimensions of stigma *(anticipated, experienced, community)*, validated measures of hypothesized interpersonal, psychological, and mental health mechanisms, measures of *other intersecting stigmas and discrimination* (due to race, gender, and socio-economic status), as well as hair samples for assessment of cortisol (a biomarker for chronic stress). We propose the following specific aims:

AIM 1) To elucidate longitudinal associations between internalized HIV-related stigma, women's adherence to HIV treatment recommendations, and corresponding immunologic and virologic outcomes in the entire national WIHS cohort, and *to examine factors underlying geographic differences in these associations*.

AIM 2) To examine the effects of additional dimensions of HIV-related stigma (experienced, anticipated, and community) on adherence and HIV clinical outcomes, and to elucidate potential interpersonal, psychological, mental health, and biological mediating mechanisms in the relationships between dimensions of stigma, adherence, and HIV outcomes, using additional quantitative longitudinal data collected at 3 WIHS sites.

AIM 3) To examine the link between intersectional stigma—including stigma related to HIV, race/ethnicity, poverty, and gender—and adherence to HIV treatment recommendations using mixed methods research.

The findings from this study will have important theoretical implications for the field of stigma research and will provide crucial information for policy and programs aiming to improve outcomes for women living with HIV. Knowledge about the effects of specific dimensions of stigma, the mechanisms for those effects, and intersectional stigma can be used to tailor interventions to maximize benefits for adherence and health.