Brief Title: The Impact of Insomnia on Pain in HIV (the HIPPI study)

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Statistical Methods. Power analysis and development of the analytic plan for Specific Aims 1 and 2 was completed with assistance from our biostatistician co-investigator for this application.

Specific Aim 1. For this aim, we assumed an effect size of 0.25, which is smaller than those observed in our preliminary data (Cohen's D range of 0.35 to 0.77). This effect size was selected to ensure that this study would be appropriately powered even if our previous work overestimated the true effect size. We do not assume that there will be an interaction effect between HIV and insomnia status, but rather an additive effect. The additive model assumes that the excess-risk for two factors (e.g., HIV and insomnia) operating simultaneously is equal to the excess risk for the first factor plus the excess risk for the second factor. Thus, our statistical model for examining the impact of insomnia on pain, inflammation, and physical function in PLWH is a factorial ANCOVA. We set our individual test Type 1 error at 0.025, which is a Bonferroni corrected value based on two tests (HIV and insomnia status) and overall Type 1 error of 5%. With these assumptions and 90% power, we will need 200 participants total with 50 participants in each group created by combining HIV and insomnia status (50 PLWH with insomnia, 50 PLWH without insomnia, 50 non-HIV with insomnia, and 50 non-HIV without insomnia). A total of 240 participants will be recruited to allow for 20% attrition.

Data analysis will begin with calculating and comparing measures of central tendency (sample mean, sample median) and dispersion (sample variance, interquartile range) for all measures of pain sensitivity (e.g., threshold, tolerance, temporal summation, conditioned pain modulation) and markers of inflammatory reactivity. Non-normally distributed data will be transformed using a logarithmic function as needed. Differences in pain sensitivity (*hypothesis 1a*) adjusting for confounding factors will be examined using analysis of covariance (ANCOVA). Post-hoc pairwise contrasts amongst groups (PLWH with and without insomnia, non-HIV individuals with and without insomnia) will be completed correcting for multiple comparisons, as presented in the sample size calculation. Additionally, linear mixed models (LMMs), containing at least random intercepts and time slopes per participant, will be employed to examine inflammatory cytokine reactivity to the painful stimuli (*hypothesis 1b*). Additional fixed effects (up to cubic polynomials) will be included to determine associations among pain sensitivity and inflammatory marker reactivity.

Specific Aim 2. It is anticipated that the 120 participants with insomnia (60 PLWH, 60 non-HIV) identified through Specific Aim 1 will matriculate through this portion of the protocol. Allowing for 20% attrition over the course of the 6-week observation period, we anticipate that 100 participants will complete all procedures included in Specific Aim 2. Using the methods of Diggle et al, this sample size would allow us to detect a difference in slopes of 0.25 of a standard deviation with 90% power. For example, we can detect a difference in the linear association of pain severity and time between PLWH with insomnia and non-HIV individuals with insomnia of 1.5 (0.25 times a standard deviation of 6.

Generalized linear mixed models (GLMMs) will be performed to address the hypotheses for Specific Aim 2. For data that appear normally distributed, LMMs will be used and the appropriate GLMM will be used for non-normal outcomes. Associations between time and outcomes (pain severity, inflammation, physical function) will be compared between PLWH and non-HIV participants with insomnia according to time by group interactions (*hypothesis 2a*). Insomnia burden for each week of the study will be categorized as "high" and "low" burden and a main effect for this designation and interaction with HIV status will be included in a model for each outcome (*hypothesis 2b*). Lastly, inflammatory marker (previously outcomes) associations with pain severity and physical functioning will be assessed in separate models (*hypothesis 2c*). All models will include potential confounders as appropriate and all assumptions for LMMs or GLMMs will be assessed. No changes in these analyses are planned due to missing data as both types of models are appropriate when data are missing-at-random.