Obstructive Sleep Apnea Endotypes and Impact on Phenotypes of People Living With HIV

Statistical Analysis Plan

NCT03575143

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Statistical Considerations:
Results will be reported as point estimates (odds ratios or mean differences across groups, as appropriate) and interval estimates (95% confidence intervals). All tests of significance for the secondary outcomes will be 2-sided and Bonferroni adjustments will be made for multiple comparisons as appropriate. A p-value of 0.05 will be considered statistically significant. Statistical analysis will be conducted using the statistical software R 3.3.3. (www.rproject.org). Demographic and baseline characteristics will be compared among the cases and controls using Fisher's exact test for categorical variables, and a two-sample t-test for continuous variables. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail.

Aim 1 – Sleep and Activity Phenotyping
To compare the symptoms of PLWH+OSA vs. PLWH–OSA. This aim will allow us to test the hypothesis that fatigue is overexpressed in PLWH+OSA compared to PLWH-OSA, independent of known covariates.

Sample Size Justification: The study is expected to enroll 120 evaluable HIV subjects, not known to have OSA, or not on treatment for OSA, and not known to have any other sleep disorder (such as narcolepsy) other than symptoms of insomnia. Based on the literature cited above, we expect to find a 50% prevalence of OSA (defined as an AHI >5/hour using 4% criteria) such that 60 subjects will have OSA and 60 will not. FACIT-F scores in HIV have been reported by two groups with remarkably similar means and standard deviations (Ref 64, 108). The presence of witnessed apneas was associated with a 6.5 reduction in FACIT score (with 3 points considered clinically meaningful, lower scores are associated with worse fatigue). Therefore, assuming a mean FACIT-F score of 36 in those without OSA and 30 in those with OSA, and a standard deviation of 12 in both groups, we will have approximately 80% statistical power to detect a difference between the two groups. Power is based on a two-sided, two-sample t-test, assuming alpha is set to 0.05. To account for 10% attrition, we will enroll 134 subjects to achieve 120 evaluable subjects.

Statistical Analysis Plan: First, we will evaluate if there is a difference in the primary outcome, FACIT-F scores, between OSA and non-OSA participants using a two-sample t-test. Multiple regression modeling will be used to assess the association between FACIT-F scores and OSA status (dichotomous independent variable), adjusting for other potential covariates, such as age, OSA severity (AHI), medications, mean sleep duration as assessed by actigraphy, and inflammation as assessed by CRP or similar such as IL-6.

Aim 2 – OSA Endotyping
Data Analysis: From the research PSG, the upper airway collapsibility as defined by the critical closing pressure (Pcrit) will be analyzed according to published methods. Additionally, the relevant traits will be extracted with the aid of MATLAB (Natick, MA) and our custom software. The traits will then be plotted on the axes ventilation vs. ventilatory demand to produce an individual assessment of the relevant traits for each subject

Aim 2: In those PLWH found to have OSA, we will perform detailed physiological assessments to determine endotype. This aim will allow us to test the following hypotheses:

> Hypothesis 2A: To compare neurocognitive performance (PVT) in PLWH+OSA with a low arousal threshold (wake up too easily) vs. those with a high arousal threshold. This aim will allow us to test mechanistically the hypothesis that stratified for similar disease

severity, low arousal threshold induced OSA yields worse neurocognitive dysfunction compared to equal severity OSA with high arousal threshold.

Hypothesis 2B: To compare endothelial dysfunction via arterial tonometry in PLWH and OSA with a high loop gain (ventilatory instability with associated hypoxemia/hypercapnia) vs. those with low LG. This aim will allow us to test the hypothesis that stratified for similar disease severity, LG-induced OSA yields worse endothelial function compared to equal severity OSA with low LG.

Sample Size Justification: Of the 120 PLWH studied in Aim 1, we believe that at least 60 will have OSA. We will split the cohort of those with OSA into high and low arousal threshold at the median value for the group. Although we will have multiple markers of cognitive function, our main outcome for Aim 2A for statistical purposes will be the psychomotor vigilance test (PVT). Prior work by Kribbs and colleagues reported a mean reciprocal reaction time of 3.9 seconds^{-1} with a standard deviation of 0.5 (Ref 112). We believe that a change of 0.3 seconds^{-1} represents a clinically important difference based on the effect size of CPAP observed with prior studies (Ref 123). Therefore, assuming a mean reciprocal reaction time of 3.9 seconds^{-1} in those with low arousal threshold OSA and 4.2 seconds^{-1} in those with high arousal threshold OSA, and a SD of 0.5 in both groups, we will have adequate power (beta >0.8) to detect a difference between the two groups (alpha = 0.05).

Statistical Analysis Plan: We will evaluate if there is a difference in PVT in OSA participants with low vs high AT using a two-sample t-test. As a sensitivity analysis, we will consider multiple regression models adjusting for additional covariates such as age, AHI, medications, mean sleep duration via actigraphy, and inflammation as assessed by CRP or IL-6 may be included in the modeling if significantly associated with outcome ($p<0.10$).

Aim 3 – Impact of OSA treatment on Sleep and Activity Phenotypes

To test in PLWH+OSA whether 3 months of PAP treatment results in changes in OSA manifestations. This aim will allow us to test the hypothesis that endotype underlying OSA will be predictive of the specific clinical improvements seen in adherent users of PAP therapy. For example, those with high LG at baseline will have the greatest improvement in endothelial dysfunction with PAP therapy compared to other OSA patients with similar disease severity as measured by AHI.

Statistical Analysis Plan: To test change over time after 3 months of PAP therapy in the PLWH+OSA group, we will compare endothelial dysfunction (EndoPAT) at baseline verses 3 months via a paired t-test. Based on Itzhaki and colleagues, we anticipate a mean endothelial function of 1.77 (SD 0.4) in those with untreated OSA, and that a delta of 0.3 represents a clinically important difference based on the effect size of treatment of OSA observed in our prior studies (Ref 127). Assuming a change in mean endothelial function of 0.5 in those with high LG induced OSA vs a change of just 0.2 in those with low LG OSA, we will have adequate power (beta >0.82) to detect this difference between the two groups (alpha = 0.05). As a sensitivity analysis, we will consider multiple regression models adjusting for additional covariates such as age, AHI, medications, mean sleep duration as assessed by actigraphy, and inflammation as assessed by CRP or IL-6 may be included in the modeling if significantly associated with outcome ($p<0.10$).

References

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