ORIGINAL ARTICLE

Effect of the duration of protease inhibitor therapy in HIV-infected individuals on the severity of obstructive sleep apnea

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Background: Protease inhibitors (PIs) are a vital part of the antiretroviral therapy. Long-term use of PIs may cause lipodystrophy, a clinical syndrome characterized by peripheral lipoatrophy and central fat accumulation, which may increase the risk of developing obstructive sleep apnea (OSA) in HIV-infected patients. We hypothesize that a longer duration of PIs' use might be associated with increasing severity of OSA in HIV-infected patients. **Materials and Methods:** This was a retrospective cohort study of HIV-infected patients who were treated with PIs, who presented with symptoms suggestive of OSA, and underwent nocturnal polysomnography. The primary objective of the study is to evaluate the association between the duration of PIs' use and the severity of OSA. The duration of PIs' use measured in months was recorded for each patient. The primary outcome of interest was the apnea–hypopnea index (AHI) obtained at the time of the sleep study. Data were analyzed using univariate and multivariate linear regression between AHIs with PIs' use as well as other predictors. **Results:** A total of 54 patients diagnosed with HIV and OSA were included in the study cohort for the analysis. Sleep study body mass index (BMI; $P = 0.042$) and change in BMI (ΔBMI; $P = 0.027$) were the only statistically significant independent predictors of AHI. The association between AHI and PIs' use duration was found to be nonlinear and nonsignificant. Gender differences evaluation suggested possible duration-related effect relationship between PIs and OSA severity among HIV-infected men exposed to PIs within a 66-month duration. **Conclusion:** We did not observe a significant association between PIs' use duration and the severity of OSA.

Key words: HIV, lipodystrophy, obstructive sleep apnea, protease inhibitors

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INTRODUCTION

Obstructive sleep apnea (OSA) is defined by recurrent episodes of upper airway narrowing or obstruction during sleep, leading to marked reduction or cessation of airflow, recurrent arousals, and oxygen desaturations.

It is a common disease in the United States, affecting 15% of men and 9% of women between the ages of 30 years and 60 years and is significantly higher in people above the age of 65. The risk of developing OSA tends to increase with obesity and increasing neck size in both males and females.[1,2]

Untreated OSA is associated with systemic hypertension, coronary artery disease, stroke, atrial fibrillation, increased motor vehicle accidents, congestive heart failure, excessive daytime sleepiness, decreased quality of life, and increased mortality.[2]

OSA has been rarely studied in patients living with HIV infection. In a recent prevalence study by Kunisaki *et al*., the prevalence of OSA in HIV-infected patients

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was 4% compared to 12% in noninfected individuals.[3] An older study by Epstein *et al*. had a reported OSA prevalence of 7% among patients with HIV.[4] On the other hand, Patil *et al*. reported an unexpectedly high prevalence of sleep-disordered breathing among HIV-infected individuals, around 70%, irrespective of their use of antiretroviral therapy.[5]

Protease inhibitors (PIs) are a key component of antiretroviral therapy and have dramatically improved the life expectancy of the HIV-infected population. The success of PIs is tempered by the appearance of adverse effects due to long-term use. In particular, PI-related metabolic disorders include lipodystrophy, a syndrome of peripheral fat wasting, central adiposity, hyperlipidemia, and insulin resistance.[6-11]

A consequence of both antiretroviral therapy-associated weight gain and PI-related lipodystrophy may pose an increased risk for OSA. Although several studies have shown a clear association of PIs and lipodystrophy in HIV patients, little data exist to explore the relationship between PIs' use or lipodystrophy and OSA. In this study, we sought to identify patients with HIV infection to determine the association between PIs' exposure and the severity of OSA among HIV patients. We hypothesized that longer duration of PIs' use might be associated with the severity of OSA in HIV-infected patients.

MATERIALS AND METHODS

Data design and settings

Our study is an observational retrospective cohort study of HIV-infected patients at the Peter Ho Clinic, a large HIV clinic affiliated with Saint Michael's Medical Center in Newark, New Jersey, USA. After getting approval from the local Institutional Review Board, the electronic medical records for HIV patients referred between 2004 and 2013 to the sleep laboratory for overnight polysomnography (PSG) were reviewed.

Study population

Based on the initial records review, we assembled a base cohort of 120 patients that included all the patients with HIV who were referred for evaluation of snoring, witnessed apneas, and excessive daytime sleepiness measured using the Epworth Sleepiness Scale (ESS); a clinician-administered sleep survey designed to detect excessive daytime sleepiness. An ESS score of ≥10 on a 24-point scale is highly suggestive of excessive daytime sleepiness, which is a key symptom in OSA.

Our inclusion criteria included patients with HIV infection, aged 18 years and older, who were treated with PIs for a minimum period of 6 months, reported compliance with treatment, and had PSG for the evaluation of OSA. Patients with age <18 years or >85 years, advanced chronic obstructive pulmonary disease or persistent asthma, noncompliance with PIs therapy, had a treatment duration of <6 months, or incomplete data were excluded from the study.

Of 120 patients in the base cohort, 54 patients met our inclusion criteria to be in the final study cohort analysis. The majority of the patients were excluded from the study due to noncompliance with PIs' use, as illustrated in Figure 1. The data for the study cohort were recorded in an abstraction form, obtaining the demographic data, which included age, gender, and race, and clinical data, including current antiretroviral medication regimen and the duration of PIs' exposure measured in months. Baseline body mass index (BMI) was obtained for all the patients (defined as the BMI at the first visit to the HIV clinic in our study) and later at the time of sleep study, as well as comorbidities aside from HIV.

Several parameters around the time of PSG were recorded including BMI (PSG BMI) and neck circumference. During the study, apnea–hypopnea index (AHI) was recorded among other polysomnographic data. The sleep study was analyzed by one board-certified sleep physician to eliminate the interobserver variability.

Statistical analysis

Descriptive summary of patients' demographic, anthropometric, and sleep study parameters was calculated, using mean and standard deviation (SD) for continuous measures and counts and percentages for categorical measures. For AHI which is not normally distributed, median and interquartile range were calculated, and nonparametric tests were used for comparison between the stratification groups. Data were analyzed initially using univariate linear regression between AHI with PIs' use duration to investigate the potential association of PI's use with AHI followed by multivariate regression to adjust for the potential predictors that may affect AHI. A two-tailed $P \leq 0.05$

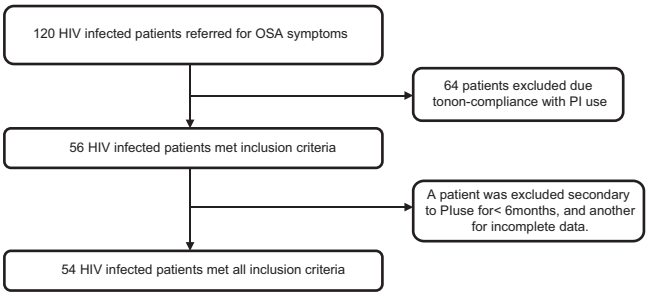

Figure 1: Flowchart of patients with HIV underwent screening for obstructive sleep apnea

is considered statistically significant. The above statistical analyses were all conducted using Stata 14 (Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP).

RESULTS

A total of 54 patients diagnosed with HIV who presented with symptoms suggestive of OSA were included in the study cohort for the analysis. The collected data are summarized in Table 1. The mean (±SD) age of patients was 49.9 ± 9.8 years. Almost half of them were men (48%). Two-thirds of the study population were African American (65%). Mean baseline BMI before PI treatment was 32.1 kg/m^2 and mean BMI before sleep study was 34.9 kg/m^2. Mean BMI difference (Δ_{BMI}) between the baseline BMI and the BMI at the time of the sleep study was 2.8 ($P < 0.00001$). The average neck circumference at the time of the sleep study was 16 inches. The study cohort had an average PIs' use duration of 60.16 months.

As expected for the outcome variable, AHI was found to have a nonnormal distribution. Upon stratification by gender, the distribution among males and females was noted to be dissimilar [Figure 2]. AHI median of 14.55/h along with interquartile range (6.3–31.1) was calculated as opposed to mean and SD; furthermore, nonparametric tests among comparison groups were performed.

Several studies in the literature report significant gender differences in OSA pathophysiology. Stratification by sex was done to evaluate for gender-related differences in our study cohort. *P* value for the median of AHI was calculated using rank sum test. *P* value for the mean of the other normally distributed continuous variables was calculated with the use of Student's *t*-test.

Both neck circumference and BMI at the time of sleep study seem to be significantly different between the two gender groups (16.7 inches and 32.7 for males, 15.38 inches and 37.1 for females with $P = 0.042$ and 0.007, respectively).

Based on the primary outcome AHI, 9 patients were found to have no evidence of OSA (AHI: <5/h), 19 patients had mild OSA (AHI: 5–14/h), 12 patients had moderate OSA (AHI: 15–29/h), and 14 patients had severe OSA (AHI: ≥30/h). To investigate the possible association of PI's use

Table 1: Characteristics and clinical data for the study cohort patients

	Patients (*n*=54)*	Stratification by sex		*P*†
		Male (*n*=26)**	Female (*n*=28)**	
Age (year), mean±SD	49.9±9.8	51.1±1.7	48.9±2.0	0.422
Race				
African American, *n* (%)	35 (65)	15 (58)	20 (71)	
Hispanic, *n* (%)	17 (31)	11 (42)	6 (22)	
White, *n* (%)	2 (4)	0 (NA)	2 (7)	
Hepatitis B (%)	5 (10)	3 (12)	2 (7)	0.663
Hepatitis C (%)	16 (30)	10 (38)	6 (21)	0.236
Hypertension (%)	39 (72)	18 (69)	21 (75)	0.764
Dyslipidemia (%)	10 (19)	6 (23)	4 (14)	0.494
Diabetes (%)	8 (15)	3 (12)	5 (18)	0.706
CHF (%)	3 (6)	0	3 (11)	0.237
Baseline BMI	32.1±7.88	30.6±1.2	33.5±1.7	0.176
PSG BMI	**34.9±8.0**	**32.7±1.4**	**37.1±1.5**	**0.042**
Δ BMI	2.85±4.65	2.1±0.6	3.5±1.1	0.255
Neck circumference	**16±1.85**	**16.7±0.4**	**15.38±0.3**	**0.007**
CD4 T-cell count	585.3±315.6	516.8±54.1	648.9±64.4	0.125
PI duration	60.16±36.8	67±6.8	53.82±7.2	0.191
OSA severity (%)				
No OSA	9 (17)	2 (7)	7 (25)	
Mild	19 (35)	7 (27)	12 (43)	
Moderate	12 (22)	8 (31)	4 (14)	
Severe	14 (26)	9 (35)	5 (18)	
Median AHI (IQR)	14.55 (6.3-31.1)	23.15 (10.8-83.4)	9.95 (4.95-17.25)	0.03

*Plus-minus values are means±SD; **Plus-minus values are means±SEM; †*P* values are for the comparison between the groups after stratification by sex. *P* value for the mean of the normally distributed continuous variables (age, BMI, neck circumference, CD4, and PI use duration) was calculated with the use of Student's *t*-test; *P* value for the skewed variable (AHI) median was calculated with the use of rank sum test and for binary variables with the use of Chi-square tests or Fisher's exact tests based on the sample size. Data in bold indicate variables with $P<0.05$ for the comparison groups. SD=Standard deviation; SEM=Standard error of mean; CHF=Chronic heart failure; PSG=Polysomnography; BMI=Body mass index at the time of PSG; AHI=Apnea-hypopnea index; IQR=Interquartile range; PI=Protease inhibitor; OSA=Obstructive sleep apnea; NA=Not available; CD=Cluster of Differentiation

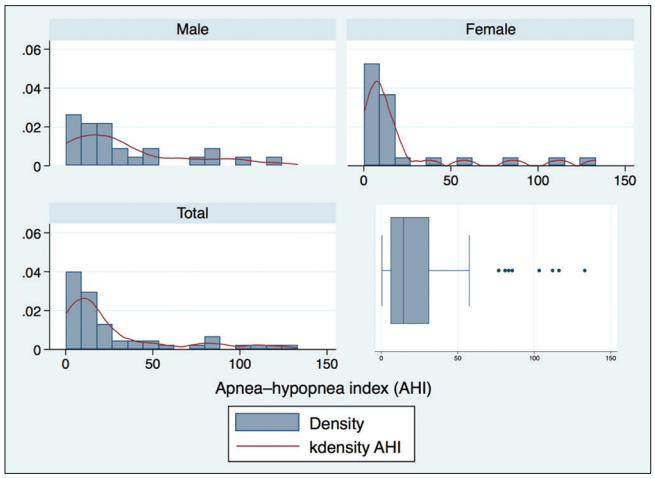

Figure 2: The distribution of apnea–hypopnea index in the study population

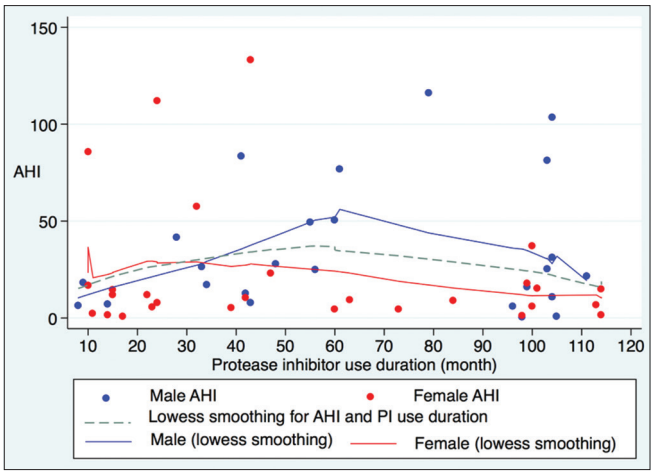

Figure 3: The association between apnea–hypopnea index and PI's use duration, using locally weighted scatterplot smoothing

duration with AHI, data were analyzed using univariate linear regression between AHIs with PI's use duration. There was no significant association found between the two variables.

It is well known that age, gender, neck circumference, and BMI are risk factors and potential predictors of AHI in patients with OSA. Univariate linear regression analyses between AHI and each of the potential variables in our study cohort (age, sex, race, neck circumference, baseline BMI, PSG BMI, and BMI difference) revealed that PSG BMI (coefficient 1.16, $P = 0.042$) and ΔBMI (coefficient = 2.1, $P = 0.027$) were the only independent predictors of AHI. Interestingly, there was no significant association between AHI and baseline BMI (coefficient 0.44, $P = 0.42$) for sex, age, race, or neck circumference.

Multivariate regression was performed for AHI (as the outcome variable) with age, sex, race, neck circumference, PSG BMI, and PIs' duration as predictor variables. Baseline BMI was omitted from the multivariate model secondary to collinearity. BMI continued to be a strong predictor of AHI in the multivariable model (coefficient 1.92, $P = 0.021$) adjusting for the above-mentioned predictors. PIs' use duration again did not reach statistical significance ($P = 0.63$). There were no statistically significant differences in AHI based on age, race, and neck circumference in our study cohort.

A nonlinear association between AHI and PI's use duration was suspected and explored using locally weighted scatterplot smoothing (LOWESS) for the whole cohort and for the two gender-related comparison groups [Figure 3]. Examining the LOWESS line for the entire cohort, we observed an increasing trend for AHI with time from baseline until certain PI's use time point (peak) followed by a decreasing trend of AHI subsequent time points.

Based on the LOWESS line, the relationship between PI's use duration and AHI in men appears to follow an inverted V-shaped function, i.e., higher levels of AHI initially associated with increased duration, but after a certain cutoff is reached; longer duration is associated with decreased AHI. Examining the LOWESS line revealed that cutoff falls between 60 and 70 months. A cutoff of 66 months (5.5 years) was chosen to evaluate the relationship between the AHI and PIs' duration in the gender comparison groups. After stratification by sex and the chosen cutoff, there was a strong correlation between AHI and PIs' use duration ($P = 0.038$, $R^2 = 0.31$) in HIV-infected men at the 66-month cutoff [Figure 4]. Within this group and interval, the model indicates that the duration of PIs' use could explain 31% of the AHI. In contrast, there was no significant association in HIV-infected women at any duration cutoff.

DISCUSSION

Lipodystrophy is a subjective clinical diagnosis, characterized by peripheral lipoatrophy and central fat redistribution. It is usually reported by the patient or found on physical examination. In the HIV-infected population, it occurs almost exclusively in patients treated with PIs and has not been reported in patients with long-standing, untreated HIV infection even in the presence of high HIV viral load in the blood.[8]

PIs have been known to cause lipodystrophy.[12-14] The reported PI -induced morphological changes include wasting of extremities, centripetal or breast fat accumulation, dorsocervical fat pad enlargement, and metabolic abnormalities including increased triglycerides and cholesterol levels.[15] It is suggested that the risk of developing lipodystrophy is directly proportional to the duration of exposure to PIs.[11] Such changes in morphology

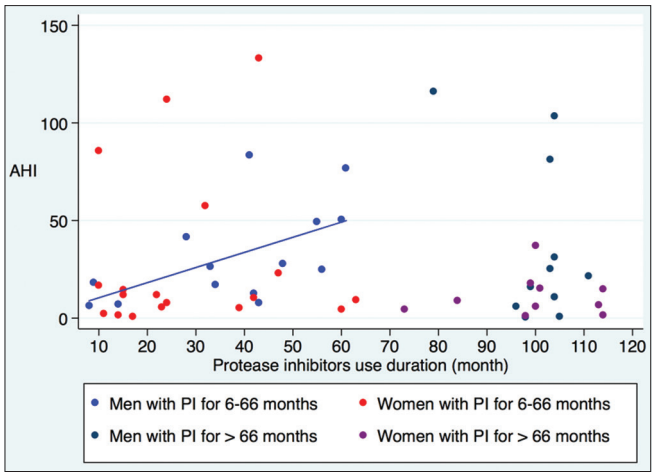

Figure 4: Correlation between apnea–hypopnea index and pulsatility index use in months in HIV-infected men at the 66-month cutoff (blue dots and trend line)

have been shown to affect the psychosocial aspects of life and adherence to medications in HIV patients.[15-17]

OSA is typically suspected in patients with older age, obesity, large neck circumference, snoring, and excessive daytime sleepiness.[18-21] It appears that such risk factors are not as important in HIV-infected individuals. Patil *et al*. reported that patients with HIV who had OSA were younger and substantially leaner, and current or prior antiretroviral therapy use was associated with an increased prevalence of OSA compared to those who had no prior exposure to antiretroviral therapy (90% vs. 57%).[5] It has been postulated that lipodystrophy might play a role in increasing the prevalence of OSA in patients with HIV, leading to upper airway narrowing in the absence of obesity.[22]

To our knowledge, this is the first study directly related to evaluating the relation between PI's exposure and its relation to the severity of OSA. Our findings showed that BMI at the time of the sleep study and ΔBMI are strong predictors of AHI in HIV-infected patients which are consistent with the available evidence for the general population. We found no evidence to confirm that a longer duration of PIs is associated with increasing severity of OSA in this cohort.

Interestingly, data analysis in male HIV patients suggests a steady rapid increase in AHI with time to a peak followed by a steady decline. It is reasonable to speculate that in HIV male patients treated with antiretroviral therapy and PIs, the increasing rates of weight gain/obesity and morphological changes of lipodystrophy due to prolonged lifetime PIs' exposure might increase the risk of developing or worsening OSA. One study reported 12 HIV patients with OSA, of which, 11 were overweight or obese and 7 had documented lipodystrophy.[23]

Our findings must be interpreted in light of our study limitations. First, this is a retrospective study with a small sample size, which limits our ability to make conclusive statements or to generate reasonable size stratification groups. Second, compliance with treatment was patient reported. Furthermore, there is one race predominance in our study which makes the findings nongeneralizable. We hope that our findings will trigger interest in future studies to clarify the nature of association between PIs' use and OSA severity. As lipodystrophy was not documented in the medical records analyzed, we are unable to evaluate the direct effect of lipodystrophy on AHI.

CONCLUSION

We found no evidence of a significant association between PIs' use duration and the severity of OSA in HIV patients within our study cohort. One interesting observation suggests a statistically significant duration-related effect relationship between PIs and OSA severity among HIV-infected men exposed to PIs within 66-month duration followed by a steady decline in AHI beyond that cutoff. It is not clear whether if this finding is reproducible in different HIV populations or unique to this small sample size cohort. Further studies are needed to clarify the nature of association in larger multi-ethnic HIV cohort.

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Conflicts of interest
There are no conflicts of interest.

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