Does HIV Really Augment the Frequency or Mortality Risk of Increased Pulmonary Artery Systolic Pressures?

In the United States, about 49% of the 1.2 million persons living with HIV infection have their circulating HIV viral load durably suppressed by antiretroviral therapy (1). Modeling suggests that such individuals could have life expectancies of 74 years compared with 80 years for the general population (2). Although improved survival for persons with HIV infection is indeed good news, an important question is whether these projections will be accurate. It is well documented that persons with HIV infection, even if virologically suppressed, have enhanced states of inflammation as measured by elevated C-reactive protein, D-dimer, IL-6, and other proinflammatory cytokine concentrations (3). An enhanced inflammatory state likely accelerates progression of comorbidities and could make estimates of survival overly optimistic.

It is instructive to look at the causes of death in persons whose HIV viral load is below the current level of detection. Three recent studies suggest that cardiovascular disease has joined liver disease and malignant neoplasms as the major causes of death (4–6). Readers of this journal are likely familiar with literature suggesting that persons with HIV infection and durable HIV viral suppression have enhanced risks of coronary artery and cerebrovascular disease, not all of which is attributable to traditional risk factors such as tobacco use, hypertension, dyslipidemia, and diabetes. Readers might not be as familiar with literature suggesting an association of HIV infection with sudden cardiac death, diastolic dysfunction, atrial fibrillation, and pulmonary hypertension (7–10).

In this issue of the *Journal* (pp. 923–932), Brittain and colleagues report their investigation of the frequency and clinical significance of elevated pulmonary artery systolic pressure (PASP) in VACS (Veterans Aging Cohort Study) (11). They studied a convenience sample of patients who were referred for any reason for echocardiography between 2003 and 2012 and compared those individuals with HIV infection with matched control subjects without HIV infection.

Only those veterans with a reported PASP measured by echocardiogram were included. Measurements of PASP and left ventricular ejection fraction range were obtained using a custom information extraction system. Although additional echocardiographic data such as diastolic function and right ventricular function would have been informative, most of these data had significant missing values or could not be obtained. Patients were followed for an average of 4 years. No clinical data on causes of death were provided.

Are elevated PASPs more frequent among persons with HIV infection who are durably suppressed by a variety of antiretroviral regimens than in matched control subjects without HIV infection? The paper by Brittain and colleagues clearly states that PASP values were similar between veterans with HIV infection and veterans without HIV infection (36 ± 15 mm Hg vs. 36 ± 14 mm Hg; $P = 0.99$), as was the prevalence of increased PASP (28% vs. 27%, respectively; $P = 0.58$).

We know that HIV infection is an independent risk factor for the occurrence and impact of coronary artery disease. Are the effects of HIV and PASP additive in contributing to mortality, or are they synergistic?

Table 3 of the paper by Brittain and colleagues demonstrates fully adjusted mortality risks for patients with and without elevated PASPs and with and without HIV infection. The authors did not calculate the difference in mortality risk that elevated PASP confers on persons with versus those without HIV infection. A back-of-the-envelope calculation suggests that the effect of HIV infection among veterans with PASP greater than 40 mm Hg is 1.18 (95% confidence interval [CI], 1.00–1.39) for the entire group and 1.77 (95% CI, 0.82–3.83) for the subgroup with no prevalent comorbidities. These confidence intervals overlap with those for veterans with PASP less than or equal to 40 mm Hg, who have mortality risks of 1.35 (95% CI, 1.21–1.50) for the entire group and 2.06 (95% CI, 1.45–2.94) for the subgroup with no comorbidities. Therefore, the effects of HIV and PASP greater than 40 mm Hg appear to be additive, but there is no statistical evidence that elevated PASP exacerbates the impact of HIV on mortality. Of course, there are no data in this study about the causes of death in these patients.

The article by Brittain and colleagues provides considerable data about the prevalence of elevated PASP in this selected population. It would be instructive to have more information about left atrial size, left ventricular mass, diastolic function, and right ventricular function. At higher PASPs consistent with pulmonary hypertension, an estimated resting PASP is less relevant than determinants of right ventricular function in terms of prognosis (12).

None of the available data provide compelling evidence that persons with HIV infection should be screened or treated any differently for such elevated pulmonary artery pressures, although there is always the caveat that drug–drug interactions must be carefully assessed when any new drugs are prescribed for persons receiving antiretroviral therapy. Future work delineating the causes of death for persons with HIV infection who have elevated PASP, assessing related morbidity, and improving our understanding of the biological basis for HIV as a possible cause of PASP elevation or as an exacerbating factor would be welcome. A precision medicine approach (13) linking phenotypes with biological mechanisms might be useful to delineate risk factors, causality, and mortality. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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This work was supported by the Intramural Research Program of the NHLBI and by the NIH Clinical Center.

Originally Published in Press as DOI: 10.1164/rccm.201711-2271ED on December 5, 2017

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Is It Time to Consider Obstructive Sleep Apnea Syndrome a Risk Factor for Alzheimer's Disease?

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder that has several consequences. As was recently documented, the prevalence of moderate-to-severe sleep-disordered breathing (≥ 15 events/h) is 23.4% in women and 49.7% in men (1). These data, from a population-based study in Switzerland, reveal the real incidence of OSAS in the general population. OSAS has been consistently demonstrated to be a clinically relevant chronic sleep disorder characterized by recurrent episodes of upper-airway obstruction causing intermittent hypoxemia and hypercapnia, brain cortical microarousals and sleep fragmentation, increased inflammation, and oxidative stress (2). These features of OSAS have significant cardiovascular, neurocognitive, and metabolic consequences. Consequently, OSAS has been independently associated with several disorders, including hypertension, diabetes, metabolic syndrome, osteoporosis, and cardiovascular diseases (3–7). Moreover, OSAS has been identified as a risk factor for the development of Alzheimer's disease (AD) dementia (8).

Sleep disorders are currently being investigated as possible pathogenic factors that trigger neurodegenerative disorders, with particular attention being paid to their effects on AD pathology. The recent identification of the glymphatic system has led researchers to investigate the association between sleep and the risk of neurodegeneration (9). The group led by Ricardo S. Osorio has focused over the past few years on the interconnections between OSAS and AD pathology in populations of cognitively normal elderly individuals (10, 11). As a result of their investigations, OSAS

was demonstrated to be responsible for cerebrospinal fluid (CSF) AD biomarker changes in the elderly (10). Moreover, they showed that OSAS is associated not only with a pathological reduction of CSF β -amyloid₄₂ ($A\beta_{42}$) levels but also with a continuing cognitive decline in the elderly (11). This evidence has been supported by further research, and it has been hypothesized that OSAS alters brain β -amyloid metabolism and promotes amyloid plaque deposition (12, 13). Therefore, the recent scientific literature has identified OSAS as a possible risk factor for AD neurodegeneration (12, 13).

The study by Sharma and colleagues (pp. 933–943) in this issue of the *Journal* represents an important milestone in this field (14). The authors first performed a longitudinal study analyzing the effect of OSAS on both CSF $A\beta_{42}$ levels and brain amyloid burden in cognitively normal elderly subjects. Specifically, a large population of cognitively intact people (55–90 yr old) underwent OSAS monitoring by home polygraphic recording, followed by lumbar puncture for CSF biomarker analysis ($A\beta_{42}$ and tau protein levels), and/or Pittsburgh compound positron emission tomography scans to detect brain amyloid deposition. These assessments were longitudinally repeated in a subgroup of subjects who underwent follow-up investigations. The main result of this study was the direct correlation observed between the annual rate of change of CSF $A\beta_{42}$ concentrations and the apnea-hypopnea index. Secondly, the authors confirmed that OSAS is a frequent diagnosis in adult and older people, as it affected 53% of the entire cognitively normal community-dwelling cohort. Moreover, the authors proved that the apnea-hypopnea index has a more significant association with the longitudinal change of β -amyloid measures than the apolipoprotein E4 genotype, which is currently