

# Commentaries on Viewpoint: The ongoing need for good physiological investigation: Obstructive sleep apnea in HIV patients as a paradigm

## HIV, OBSTRUCTIVE SLEEP APNEA, AND LIPODYSTROPHY: A COMPREHENSIVE APPROACH

TO THE EDITOR: The intriguing paradigm put forth by Darquenne et al. (3) highlighted that improved therapy against human immunodeficiency virus (HIV) has come at the cost of elevated rates of chronic diseases, such as obstructive sleep apnea (OSA) and obesity, during the highly active antiretroviral therapy (HAART) era. Indeed, obesity in HIV-infected individuals, especially women, has been rising (1). In a study by Crum-Cianflone et al. (2), 63% of HIV-infected patients in multiple HIV clinics were overweight/obese. In addition, lipodystrophy in HIV patients is a likely cause of OSA (2, 5), and thus increased obesity and neck circumference in HIV patients lead to prevalence of OSA (3, 5).

We agree that understanding HIV patient populations and their respective risk factors, as suggested by Darquenne et al. (3), is essential for effective antiretroviral therapy. Specifically, it is our belief that treating obese HIV-infected individuals necessitates a more thorough understanding of lipohypertrophy predisposition, as well as pharmacological treatment options. An example carried out by Edgeworth et al. (4), which suggests the potential benefit of thiazolidinediones in lipodystrophy treatment through fat redistribution, offers a combined approach that could simultaneously manage a patient's HIV and OSA symptoms (3).

In our view, thorough studies that examine the overlap between HAART, OSA, and an individual's susceptibility to lipohypertrophy will be paramount to improving the lives of a large proportion of HIV-infected patients. However, based on preliminary results, clinical application in a large-scale setting has not yielded consistent outcomes (4).

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## COMMENT ON VIEWPOINT: "THE ONGOING NEED FOR GOOD PHYSIOLOGICAL INVESTIGATION: OBSTRUCTIVE SLEEP APNEA IN HIV PATIENTS AS A PARADIGM"

TO THE EDITOR: We congratulate Darquenne et al. (2) on their Viewpoint article highlighting the need for rigorous research investigating the relationship of obstructive sleep apnea (OSA) and human immunodeficiency virus (HIV). Such research poses a unique challenge in light of the multivariate etiology of OSA that is highly individualized (3). Yet, considering that Patil et al. (4) found that body mass index adjusted analyses marginalized the differences in sleep-disordered breathing (SDB) observed between HIV<sup>+</sup> and HIV<sup>-</sup> men, and even among HIV<sup>+</sup> men using highly active antiretroviral therapy (HAART) and those who do not, we wonder if this phenomenon warrants investigation into HAART regimens that include protease inhibitors vs. those that do not, because it is mainly the protease inhibitors as a class that induce perturbations in lipid metabolism relative to the other classes of HAART (1). Aside from lipid effects, we contend that no differences in physiology of SDB will likely be observed among HIV<sup>+</sup> (HAART<sup>+</sup> or HAART<sup>-</sup>) and HIV<sup>-</sup> individuals with appropriately adjusted analyses. Considering this point, how would management of HIV<sup>+</sup> patients with SDB differ from an HIV<sup>-</sup> individual with SDB? Therefore, it is imperative that the investigation of the integrative physiology of HIV and OSA must first address the role of BMI (quite literally, the "elephant in the room!").

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## COMMENT ON THE ONGOING NEED FOR GOOD PHYSIOLOGICAL INVESTIGATION: OBSTRUCTIVE SLEEP APNEA IN HIV PATIENTS AS A PARADIGM

TO THE EDITOR: Darquenne et al. (3) propose an interesting theoretical framework for linking HIV infection with a high prevalence of obstructive sleep apnea, emphasizing on the physiopathological role of antiretroviral therapy.

However, a first debatable and central point of discussion is that the existence of a higher prevalence of obstructive sleep apnea in HIV-infected than in uninfected patients is unsupported by existing relevant bibliography. Three recent studies in fact indicate that this would not be the case (2, 4, 5). All these studies show a prevalence of obstructive sleep apnea that is slightly higher in HIV-uninfected patients than in the HIV-infected group (5). Kunisaki et al. (4) reported a cohort of 3,641 HIV-uninfected and 3,683 HIV-infected patients, showing a prevalence of obstructive sleep apnea of 12.4 and 3.9%, respectively.

A second disputable point is to assign to antiviral therapy a major causal responsibility for obstructive sleep apnea. Untreated HIV-infected patients show a prevalence for obstructive sleep apnea that is similar to those receiving antiretroviral therapy (2, 4, 5). This may suggest that antiretroviral therapy is not a strong risk factor for development of obstructive sleep apnea. Finally, it is not reasonable to disregard the possible role of HIV associated neuroinflammation (2) and denervation (1) in the pathogenesis of obstructive sleep apnea.

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## ACTIVATION OF RENIN-ANGIOTENSIN SYSTEM: A POTENTIAL LINK BETWEEN ANTIRETROVIRAL THERAPY AND OBSTRUCTIVE SLEEP APNEA

TO THE EDITOR: The article by Darquenne and colleagues (3) highlights the importance of integrative physiology to understand different complications associated with antiretroviral therapy (ART). The authors point out that human immunodeficiency virus (HIV) infection and obstructive sleep apnea (OSA) are independently linked to increased cardiovascular disease risk. In this regard, the interaction of ART, OSA, and renin-angiotensin system (RAS) peptides needs to be considered. Chronic intermittent hypoxia (IH), a characteristic of OSA, leads to sustained elevation of sympathetic activity and blood pressure (BP) (5). In humans, the increase in blood pressure after exposure to IH is abolished by blockade of the

angiotensin II AT<sub>1R</sub>, suggesting an important role for the RAS in the pathophysiology of hypertension associated with IH (4). Endogenous angiotensin peptides acting in sympathetic premotor neurons contribute to IH-induced increases in BP observed in a model of sleep apnea-induced hypertension (2). Part of the antiretroviral therapy includes HIV protease inhibitors (PIs). The effect of PIs on the enzymatic cascade of the RAS remains to be investigated. Interestingly, evidence indicates that HIV patients using PIs develop a metabolic syndrome including insulin resistance, lipodystrophy, and hypertension and at least part of the mechanism involves activation of the RAS (1). Therefore, the choice for PIs could activate RAS exacerbating the sympathetic output in HIV patients with OSA contributing to development of cardiovascular disease. Altogether, these observations suggest a complex interaction of factors in patients under ART therapy, leading to a vicious cycle that can only be explained through integrative physiology.

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## HIV INFECTION AND OBSTRUCTIVE SLEEP APNEA: WHY EPIDEMIOLOGICAL DATA ARE NEEDED

TO THE EDITOR: The Viewpoint article makes a case that HIV-infected patients should be assessed more frequently and more carefully for obstructive sleep apnea (OSA) (1). However, as for other non-AIDS complications, international epidemiological work is needed to determine the best prevalence and incidence disease estimates. Indeed, the case of cardiovascular diseases (CVD) in HIV populations shows that such data are needed to anticipate adequate health care response as risk evolves rapidly. Large epidemiological studies have found that CVD incidence is actually decreasing in particular for arteriosclerotic disease in HIV disease. The use of less cardiotoxic antiretrovirals as well as preventative measures for CVD are probably responsible for such a decrease (5). In addition, further data show that CVD events are less likely in those who have not experienced immune depression (4).

Furthermore, a recent study (3) that was not referenced in the Viewpoint found that the prevalence of OSA in the Veterans Aging Cohort Study is lower than in age-comparable controls, even with correction for traditional OSA risk factors

(age and BMI). This further highlights the need for large international studies that rigorously assess the effect of OSA, multiple comorbidities, as well as their intricate demographic mediators (2), including survivor bias. Although we agree that optimal physiological investigation is needed in HIV-infected patients, particularly for OSA as suggested by the Viewpoint's title, the real issue is that robust epidemiological estimates of OSA prevalence and incidence are needed. This is important because there are many competing non-AIDS complications in chronic HIV infection.

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## COMMENTS ON “VIEWPOINT CALL FOR COMMENTS: THE ONGOING NEED FOR GOOD PHYSIOLOGICAL INVESTIGATION: OBSTRUCTIVE SLEEP APNEA IN HIV PATIENTS AS A PARADIGM,” ADDING CENTRAL SLEEP APNEA AND PERIODIC BREATHING TO THE PICTURE

TO THE EDITOR: We read with great interest the work from Darquenne and colleagues (1) suggesting the need of integrative physiology analysis to understand potential mechanisms for OSA in HIV patients. As mentioned by the authors, the prevalence of OSA among HIV-infected persons has been surprisingly high even among those who are not obese. Knowing that among other complications, HIV patients experience instability in ventilatory control and neurological damages and that HIV infection is associated with impaired cardiovascular risk, we suggest that periodic breathing might also play a key factor in the observed amount of SDB in HIV patients. This might look contradictory given the low proportion of central events ( $11 \pm 20\%$ ) observed in HIV patients by Patil and

colleagues (4). It should be noted that although several authors such as Tkacova and colleagues (5) have already concluded that in some patients with heart failure, OSA and CSA are part of a spectrum of periodic breathing that can shift over time. In another study by Hoffman and Schulman (3) on the appearance of CSA after treatment of OSA, the authors indicate that there is evidence that many laboratories treat respiratory events as if they were obstructive, when in fact they pathophysiologically may be closer to central. We therefore suggest the use of tools capable of detecting periodical instability beyond CSA or OSA cases (2). Once periodic breathing has been identified, the associated loop gain, or its periodicity, might open a new window of information: a wider integrative physiology approach to understand SDB in HIV patients.

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## RESPONSE TO DARQUENNE ET AL.

TO THE EDITOR: In their Viewpoint, Darquenne et al. (2) focus on the role of obstructive sleep apnea (OSA) as one non-AIDS condition complicating health issues in HIV-infected patients. Their conclusion advocates the importance of integrative physiology to understand chronic diseases with a view toward improving the lives of persons living with HIV.

We concur that understanding pathophysiologic mechanisms is essential to any contemporary biotechnological repertoire, thus emphasizing the need to follow principles derived from advances in physiology.

However, within the logic of the approach in their Viewpoint, OSA ranks low within the list of conditions following in the wake of antiretroviral therapy. With the focus on OSA alone, the problem is losing proportions because the impact of diseases such as diabetes, cardiovascular disorders, and malignancies outweigh OSA as a contributor to major health risks.

In our view, this report insufficiently captures the overall impact of reported findings. Indeed, there is a plethora of literature on the deleterious interaction of diabetes and depression alone (5) and also that between sleep orders and mental health (1). Additionally, our criticism concerns the role of symptoms such as fatigue, prevalent in HIV-infected patients as well as in large patient groups diagnosed with functional somatic syndromes (4).

Therefore, one is well advised to concede that in conditions fraught with somatic and mental health diagnoses such as HIV, any pathophysiological assessment is preferably guided by the model proposed by Engel (3). Although this paper dates from 1977, we think its ideas have lost nothing of its actuality.

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#### COMMENT ON: THE ONGOING NEED FOR GOOD PHYSIOLOGICAL INVESTIGATION: OBSTRUCTIVE SLEEP APNEA IN HIV PATIENTS AS A PARADIGM

TO THE EDITOR: The article by Darquenne et al. (2) uses sleep-related problems in HIV to illustrate their main thesis, but the principles of their Viewpoint have much broader implications. In that spirit we address another example where physiology is critical to best medical practice.

Treatment of the acute respiratory distress syndrome (ARDS) is exceptionally complex because in addition to the primary injury such as trauma, sepsis, or pneumonia that initiates the disease process, a secondary ventilator induced lung injury (VILI) is believed to drive progressive lung injury

ultimately resulting in ARDS (5). Darquenne et al. (2) highlight the essential need for good physiologic investigation to identify the mechanisms in complex pathologic diseases such as ARDS/VILI. Our group has taken a solid physiologic approach to investigating not only the mechanisms of VILI but also the possibility of developing a mechanical breath that could be used as a therapeutic tool to prevent ARDS before it develops (1, 4). Unlike reductionist studies that focus on a blocking a single molecular mediator to prevent ARDS or VILI using small animal models, we looked at the impact the mechanical breath on multiple physiologic components including: 1) lung and chest wall mechanics, 2) lung fluid balance, 3) alveolar microstrain (3), and 4) pulmonary surfactant function in a high fidelity, clinically applicable porcine ARDS model (4). We demonstrated that an extended time at inspiration and minimal time at end expiration using airway pressure release ventilation (APRV) preserves surfactant function, maintains lung fluid balance preventing edema, and normalizes lung mechanics, which when combined, prevent ARDS (4). These studies strongly support the need of an integrative physiologic approach to solve complex clinical problems; indeed our work recently showed that preemptive APRV works clinically, preventing ARDS in humans (1).

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