

Commentary on Lahiri et al. Weight and Body Mass Index Change After Switching to Integrase Inhibitors or Tenofovir Alafenamide Among Women Living with HIV

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Among women living with HIV (WLWH), increases in body weight and body mass index (BMI, kg/m²) have been observed after switching to the antiretroviral therapies (ART) - Integrase Inhibitors (INSTI) and/or Tenofovir Alafenamide (TAF) [1,2]. This has broad implications for the HIV aging process and occurrence of later-life disease. While life expectancy for people living with HIV has increased, primarily due to highly-effective ART, the course of aging with chronic HIV remains relatively unknown. Particularly of interest are long-term ART consequences on individual physiological processes and end-organ systems. Increasing BMI leads to overweight and obesity, primarily due to excess adipose tissue accumulation. This is a sincere consequence of certain ART, mostly observed with use of the newer INSTI, specifically dolutegravir, compared to other INSTI [3-6]. While mechanisms whereby INSTI cause weight gain are not well understood, HIV infection has adverse metabolic and aging-related complications that are further complicated by the overweight and obesity-related side effects of ART in societies where obesity is a chronic disease [7], and overweight and obesity are pandemic [8]. Overweight and obesity have major medical, social, and economic repercussions [8]. Consequently, we can expect more ART-related cardiovascular and cerebrovascular sequelae, as well as polypharmacy to control both HIV infection and vascular risk. The paper by Lahiri, et al. [1] offers insights into the role of ART, specifically INSTI and TAF, on simple clinical measures of body weight and BMI.

Our group's interest is the role of overweight and obesity on health of the aging brain, particularly in WLWH, and uninfected women [9-11]. Through decreases in cerebrospinal fluid HIV viral loads that reflect HIV in the

central nervous system, ART has reduced the occurrence of severe HIV-Associated Neurocognitive Disorder (HAND) [12]. With extended survival however, one must consider the occurrence of late-onset cognitive impairments and dementias, including Alzheimer's Disease and Related Dementias (ADRD), and Vascular Cognitive Impairments and Dementia (VCID) [13]. In addition, ART may induce other pathophysiological mechanisms leading to cognitive impairments and dementias *via* overweight and obesity and/or vascular and metabolic aberrations. Higher body weight, BMI, and central obesity among middle-aged, uninfected populations have been positively associated with subsequent late-onset cognitive impairments, ADRD and VCID [13-16]. Increased body weight and/or BMI among initially, non-obese INSTI and TAF users, are thus, particularly relevant when considering long-term cognitive health for people living with HIV infection. Whether WLWH will experience similar associations between overweight and obesity at middle-age and late-onset ADRD or VCID, and/or whether INSTI ART regimens further increase their risk, need to be monitored over time.

The paper by Lahiri, et al. [1] elicits several questions when considering overweight and obesity in relation to brain health. Over a follow-up period of 1-2 years, WLWH experienced body weight and BMI increases of 1-5 kg and 1-2 kg/m², respectively. This is an alarming increase if continued over decades. These observed changes were dependent on 1) initial BMI, and 2) ART switch to INSTI only or INSTI+TAF. Questions related to this include: 1) Do women who switch to certain ART regimens continue to gain body weight and BMI over time? 2) Do women reach an inflection point and subsequently decline? 3) Do women plateau at a certain level of body weight and/

or BMI? Furthermore, is there an absolute or percent gain in body weight or BMI that increases risk of cognitive impairments and ADRD later in life, both independently and/or in combination with concomitant vascular risk factors? Another issue includes control of vascular risk factors such as hypertension, hyperlipidemia or type 2 diabetes. Are medical interventions for HIV and/or vascular conditions merely compressing middle-aged morbidity? In addition, as women appear to be more affected by adverse vascular and metabolic effects of ART, does sex or gender alone pose a risk for later-life ADRD as observed in some studies of aging [17,18]? Answers to these questions may inform uninfected populations, where data are sparse on this degree of iatrogenic body weight or BMI gain over a short time. However, some Type 2 diabetes medications such as insulin, and less commonly used sulfonylureas and thiazolidinediones, cause body weight gain, while others cause weight loss or are neutral [19]. Acetylcholinesterase inhibitors used for treatment of AD cause body weight loss during a life stage when weight loss is suboptimal for healthy survival [20].

The incidence and prevalence of cognitive impairments and ADRD, including VCID is expected to triple by 2050 [13]. The debilitating and resource-consuming sequelae of overweight and obesity affecting both brain and periphery, are thus worth investigating, particularly among cognitively-vulnerable groups, such as WLWH. Understanding the short-term adverse vascular and metabolic side effects of INSTI and TAF ART, such as body weight and BMI gain, warrants close, long-term follow up to determine the lifetime vascular and metabolic profiles of patients on these regimens, and potential impact on cognition, ADRD and VCID.

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