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Non-communicable Diseases: An Epidemiological and Medical Treatment Scape: Threat of the Three-headed Hydra

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Infectious diseases are now being rivaled, and soon will be surpassed, by non-communicable diseases [1]. As a result, the United Nations have set a goal for 2025: to reduce non-communicable diseases (NCD) by 25% [1-3]. To target this burden there is a pressing need to address some of the most prevalent NCDs. As discussed in more detail later, we have selected 3 NCDs: high blood pressure (HBP), which is now recognized as "the silent killer" (head 1=affects one billion people worldwide); obesity (head 2=2.3 billion overweight adults in the world by 2015) and osteoporosis (head 3 ≥ 200 million people worldwide) [4-7].

From the epidemiological point of view, obesity is currently a major public health threat for the United States, given that this country has the second highest obesity rates in the world [8]. Obesity affects over one-third of the American adults (approximately 167 million in 2012) [9]. Even worse estimates suggest that without interventions by 2020, 75% of Americans will be overweight or obese. The medical cost of obesity in the U.S. has been estimated in $147 billion [9]. Being overweight or obese upsurges in-patient costs by 46%, and prescription-drugs by 90%. The impressive and critical impact of obesity in the next decade is hard to imagine but will likely lead to staggering costs and a significant medical burden to the US health budget, as approximately 213 million obese individuals will need services for diseases associated with obesity [10].

High blood pressure (HBP), the "silent killer" affects approximately 78 million Americans [5]. Five years ago the direct and indirect costs of hypertension were estimated at $69.9 billion. HBP is a significant risk factor for cardiovascular disease (CVD), which is the leading cause of death in women, with statistics showing that every minute in the United States, a woman dies from a cardiovascular disease [11]. Thus, it is imperative to identify, disseminate and implement more effective approaches to achieve optimal control of this condition. Accordingly, the American Heart Association has made hypertension a primary focus area of its 2014-2017 strategic plans [12].

Osteoporosis is a growing public health issue in all-aging societies, such as the United States, Europe and Japan [13]. Today, 40 million people in the United States are ages 65 and older, but this number is projected to more than double to 89 million by 2050 [14] These increases in the number of older Americans will have a profound impact on public health. Osteoporosis has escalated to what is now considered a major epidemic; the disease in the United States affects about 57 million individuals [7]. In addition, 34 million Americans have osteopenia, or reduced bone mass, increasing their risk for developing fractures at a later age [7]. As a consequence, over 2 million fractures occur each year, resulting in a 36% increased rate of mortality within one year, and an excess cost of 22 billion dollars, while the cumulative cost over the upcoming two decades has been estimated to approximately $474 billions [7,13]. In addition to a financial burden, osteoporosis takes an enormous personal and economic toll associated with pain and disability. In Europe, the disability due to osteoporosis is greater than the one caused by cancers [13].

With the increased survival achieved with 28 antiretrovirals developed in the past decades, people living with HIV (PLWH) are increasingly developing illnesses that decades ago were uncommon among this group. The fear of debilitating cacheexia has vanished, and has been replaced at a rapid pace by obesity complications [15,16]. The challenges of HIV management can be even greater when considering that obesity can exacerbate other illness, such as CVD and osteoporosis, that are already more prevalent among PLWH [16,17]. For PLWH, rates of CVD are approximately two-fold higher than for age-matched people without HIV infection [17]. More frequent reports have been published suggesting that hypertension is also increasing in PLWH [18,19]. A similar trend has been observed for osteoporosis, as increase in fracture prevalence among PLWH is up to four times greater than in age matched individuals in the general population [20-23]. Although it has been recognized that skeletal problems stem from HIV infection and disease progression, paradoxically it becomes clear that, despite ART, problems may continue unabated and are expected to increase given a rapidly aging demographic (50%>50 years old) [19,21]. These findings have important implications for fracture prevention, and indicate the urgency of identifying any modifiable risk, to avoid the vast burden to patients and society (i.e., costs, disability). Accordingly, the 2013 National Osteoporosis guidelines list HIV among risk factors that should prompt early bone screening and prevention measures [20-22]. Traditional osteoporosis risk factors commonly found in PLWH, such as smoking (40-80%), may also be contributing to this eminent problem, but the magnitude of its contribution is currently unknown. Yet, in the general population, a meta-analysis including 29 studies has concluded that approximately one in eight fractures is attributable to cigarette smoking [24]. How much is related to HIV specific factors is also a theme of debate. To our surprise, the role of hazardous alcohol use in these increased risks has been overlooked. There are many reasons to hypothesize that hazardous alcohol use would lead to worse bone health. Calcium is one of the main bone-forming minerals and hazardous alcohol use is known for inducing hypocalcemia [25,26]. Vitamin D is a secosteroids responsible for enhancing intestinal absorption of calcium and phosphate. Once converted to calcitriol, vitamin D regulates the concentration of calcium and phosphate in the bloodstream and promotes the healthy growth and remodeling of bones. Alcohol abuse is also a well-known trigger of vitamin D deficiency (defined as <20 ng/mL) [18]. Notably, central fat accumulation, which we recently reported to be linked with hazardous alcohol use, has been associated

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with lower bone marrow density in PLWH. Abnormal fat distribution may mediate bone loss through the complicated relationships between central signaling of adipocyte hormones [27]. Last but not least, pro-inflammatory cytokines, such as tumor necrosis factor alpha and interleukin 6, which are associated with osteoporosis and fractures in other populations increased significantly with HAU [20,21,28]. For the time being, clinicians should be aware of the increased risk that osteoporosis presents in this population and plan accordingly. These findings are also relevant for insurance purposes, as coverage for BMD testing should be prioritized in these at risk populations.

Furthermore, with the graying of the HIV positive and of the general populations, the rates of these diseases are expected to rise even more. The health care systems are already feeling the load of the "baby boomers", and that will strain resources in subsequent years. Older adults with HIV/AIDS will add to this burden, with rising needs related to medical complications of HIV/AIDS. The threat is further increased when considering that these are syndemics (as is the nature of the beast); so, declines in quality of life, increased needs for health care services and enhanced risks of death, are expected. How to decide, in this time of global economic crisis, which one of these scourges to tackle first? Could it be possible to lop off three heads at once? The answer is yes. In our bout against smoking and HAU in PLWH we have observed the relevance of these widespread unhealthy behaviors. First, let me highlight that while the prevalence of cigarette smoking in the United States has declined to 20%, rates of smoking among PLWH remains up to 4-times higher than that of the general population [29]. A similar trend is also observed with regards to HAU.

For PLWH, these prevalent behaviors can act as risk factors for suboptimal health. For example, while it is generally accepted that smoking “plays” a protective role against gaining weight, more and more studies worldwide have linked heavy smoking with obesity [30,31]. They also highlight a dangerous association among heavy smoking, abdominal obesity and insulin resistance [30]. So why have these discoveries been ignored? More than likely it is due to the fact that the underlying mechanisms remain largely unknown. However, we recently uncovered a significant relationship between use of mentholated cigarettes and obesity [29]. Findings are mostly related to the enhanced appetite properties of menthols. Noteworthy, industry documents indicate that since the 60's tobacco companies started experimenting with additives to control appetite(both stimulants and suppressors), to uncover a new market of smokers, and it looks like they found it [32].

Another plausible contributor to obesity is HAU, as every component of the energy-balance equation is altered by alcohol. The first alteration is in the number of calories consumed. This coupled with reduced energy expenditure facilitates weight gain in PLWH. A daily excess of energy of 100 kilocalories can lead to an accumulation of approximately 5 kg of fat in a single year [23]. Notably, a recent study has estimated that the average American adult consumes approximately 100 calories worth of alcohol daily. Alcohol can also suppress lipid oxidation, resulting in a positive fat balance [31]. Notably, non-oxidized fat tends to be deposited in the abdominal area [31]. In line with these observations, our most recent study has demonstrated that among PLWH, HAU alcohol use is associated with central obesity [15]. We also found that the frequent alterations in BDNF signaling may also be responsible for the overlap of obesity and hazardous alcohol use [15].

In the beginning of the HIV epidemic hypertension was not considered among the list of clinical concerns, though it has recently become clear that PLWH are at a higher risk than before [17,18]. Compared to controls, PLWH had a higher prevalence of hypertension (54% vs. 38%) [33]. These rates are of great concerns, given the well-known role of hypertension on the costly neurological, cardiovascular and renal diseases [5,18,19,33]. Achieving control of HBP may require current interventions that are focused on prescribing blood pressure therapy to concentrate efforts into broad prevention. In addition to HIV related factors (i.e., HIV, antiretroviral toxicity), increases in blood pressure readings are likely the combination of excess smoking, alcohol use, and increases in obesity among PLWH [33,34].

In summary, if smoking and HAU entails an excessive risk of obesity, CVD, or osteoporosis, then jointly addressing smoking and alcohol will provide an unrivalled opportunity to "head off' three diseases at once. More importantly, such interventions will allow shifting the entire distribution of risks at a population level. Accordingly, the HIV-doctor of the new millennium needs to become a "triple specialist". The HIV providers of the new era can no longer focus on juggling HIV treatments and respective toxicities. Now they need to become experts in aging-related diseases, but most important, health care providers should become active members of the prevention force in these areas. Yet, under the Affordable Care Act, third-party payers, such as private insurance companies, should be fiscally supporting obesity prevention services [10]. Hypertension treatment and management are subject to cost sharing [11,12]. So far, I've not found the codes to support the "in-person meetings per month" that are optimal for screening and treating smoking and hazardous alcohol use. Not addressing HAU, smoking and obesity in a timely fashion will undoubtedly have a significant economic and social impact that will be regretted for years to come.

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