Cardiovascular disease in HIV-infected patients: a focus on diabetes mellitus and hypertension?

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Introduction

Diabetes and hypertension are among the most important risk factors for cardiovascular disease (CVD) and mortality in the general population.[1] CVD alone accounted for nearly half of the 38 million global deaths due to non-communicable diseases (NCDs) in 2012.[2] The number of individuals with diabetes is on the increase and will rise to 366 million by 2030 globally.[3] Similarly, the global prevalence of hypertension is projected to rise to affect 1.56 billion adults by 2025.[4] However, the greatest rise in diabetes and hypertension will occur in the developing regions of the world like sub-Saharan Africa (SSA).[4–6] Unfortunately, SSA is also the region that bears a disproportionately high burden of the HIV/AIDS pandemic and struggling health systems. Of the estimated 35 million 'People Living with HIV' (PLWH) globally in 2013, SSA is home to 71% of them,[7] with about 7.5 million accessing combination antiretroviral therapy (cART) in 2012.[8] The global prevalence of HIV infection in Figure 1 shows Africa to be the most affected region with a prevalence of 4.5%.[7]

PLWH are now living longer, largely due to improving access to cART, such that HIV/AIDS is increasingly viewed as a chronic disease rather than the invariably fatal infection it once was. However, diabetes and hypertension are associated with the advanced age, as well as changing lifestyle, that come with increasing prosperity and urbanisation, as is being currently witnessed in many low- and middle-income countries.[9,10] In addition to the usual risk factors for CVD seen in the general population, PLWH may have additional risks. Endothelial dysfunction and metabolic disorders associated with chronic inflammation in HIV infection itself and the use of the very life-saving cART may be responsible for the observed excess risk for CVD.[11–13] Therefore, the stage appears set for a twin epidemic of HIV/AIDS and NCDs such as diabetes and hypertension in sub-Saharan Africa.

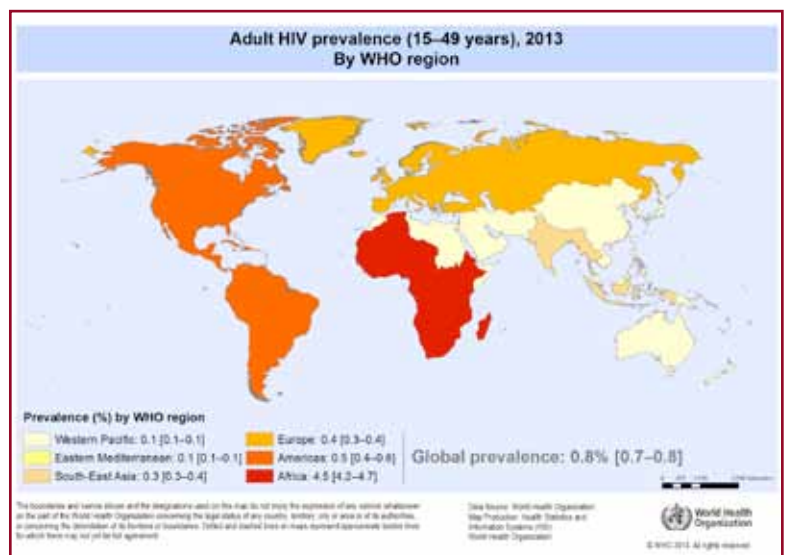An epidemic of HIV/AIDS and diabetes or hyperten-

Figure 1. The adult HIV prevalence by World Health Organization (WHO) regions in 2013 (available from: http://gamapserver.who.int/mapLibrary/Files/Maps/HIV_adult_prevalence_2013.png).

sion could stall or even reverse the improvements in morbidity and life expectancy being recorded among PLWH, and further strain the already fragile health systems. Even though diabetes and hypertension are only a part of complex and overlapping variables that confer risk for CVD and other NCDs, a focus on them is important because they share common risk factors that are preventable, easily diagnosed and treated, with an associated substantial reduction in morbidity and mortality.[14] Moreover, emerging lessons from Cambodia and Uganda show that integrating HIV/AIDS services with services for NCDs like diabetes and hypertension is feasible and beneficial.[15,16]

Emerging importance of diabetes and hypertension among PLWH

Countries with a high prevalence of HIV infection have been concerned with scaling up HIV/AIDS interventions; but will now, or in the near future, also have to contend with the spiralling burden of NCDs.[17] This assumption is supported by data that show PLWH carry substantial risk of CVD whether they live in low- or high-HIV prevalence settings. For instance, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study (a large observational study of about 18000 that has been

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recruiting mostly cART-treated patients since 1999 from hospitals across Europe, USA, and Australia) revealed that about 25% of the male and female patients in the cohort were ≥45 years and ≥55 years respectively.[18] This age cut-off has been previously described as conferring high cardiovascular risk in the general population in the National Cholesterol Education Programme guidelines[19] whereas being older than 40 years confers three times the risk of hypertension in PLWH.[20] This should be an important point to note considering that PLWH in Africa are now living longer. Furthermore, at baseline in the DAD study, more than 50% of the cohort were current cigarette smokers while about 22% had elevated total cholesterol, with triglycerides elevated in 34%. Smoking may also be prevalent among PLWH in SSA. Depending on the population studied, 3–30% were current cigarette smokers in West Africa.[21] The overall prevalences of diabetes and hypertension in the DAD study were about 2.5% and 8.0% respectively. The study also showed that regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTI) and/or protease inhibitors (PIs), which are increasingly available in Africa, were associated with hypertension in univariate analysis. Importantly, this association disappeared in the final model containing age, sex and body mass index (BMI) as co-variates.

Contrary to association with hypertension, all cART regimens were independently associated with diabetes in the study. Another 10-year cohort study[22] involving 1046 PLWH on cART which covered 7846 person-years of follow-up (PYFU) in France, reported an overall diabetes incidence of 14.1/1000 PYFU. Although the sensitive oral glucose tolerance test (OGTT) was used for diagnosis, the more diabetogenic first-generation cART that were partly responsible for this rather high incidence of diabetes are still commonly used in SSA, or are only being slowly phased out.

Data on CVD and their risk factors among PLWH in Africa are mostly from relatively small studies.[23–25] However, a Ugandan hospital-based cohort of about 5600 PLWH aged ≥13 years receiving cART reported an overall 28% hypertension prevalence and at least 10% 10-year Framingham Risk Score in a subset of men.[26] Also, a systematic review with meta-analysis involving nearly 30 000 black adults who resided in sub-Sahara Africa[27] reported differences in CVD risks between HIV-infected and HIV-negative populations that may be modified by cART.

In addition to reduced quality of life and increased treatment complexity and cost, the NCDs are now also a leading cause of mortality and are reported to be responsible for 53% of all deaths in PLWH who are older than 40 years.[28,29] Although the survival model by Braithwaite et al[28] was based on data in the USA where cART has been widely available for a long time, the current scale-up in cART in Africa is also likely to cause a shift in causes of mortality from opportunistic infections to NCDs. Nonetheless, mortality due to NCDs in PLWH may not be entirely explained by the longevity advantage conferred

by cART or the metabolic effects of cART. Lodwick et al[30] in a review of data from 23 cohorts in industrialised countries showed death rates were higher than in the general population among cART-naïve patients even when they had high CD4+ counts. This has led to suggestions that HIV itself, including differences in biological activities of viral types and strains, may play a role in the clustering of cardiovascular risk and mortality.[27] Cause-specific mortality data on NCDs among PLWH are hard to find in Africa but inferences can be drawn. Data from the Kenyan Ministry of Health reported that NCDs were responsible for 32% mortality in the general population with over 70% of the deaths due to CVD and diabetes,[31] and screening of 5800 PLWH found higher rates of hypertension than in the general population with a trend towards higher blood glucose levels.[32]

Pathogenesis of diabetes in HIV/AIDS

The development of diabetes in PLWH may be associated with traditional factors as seen in the general population, in addition to HIV-related factors and the use of cART.

The decrease in peripheral fat and increase in central fat (lipodystrophy) with perturbations in serum lipid concentrations may lead to variable levels of insulin resistance. In the mouse model, HIV accessory Vpr protein has been shown to contribute to disorders of insulin–glucose homeostasis by markedly enhancing glucocorticoid action on a wide array of response promoters.[33] The Vpr accessory protein may also induce insulin resistance or lipodystrophy by affecting the function of peroxisome-proliferator activated receptor-γ (PPAR-γ), an important regulator of adipocyte differentiation and tissue insulin sensitivity.[34]

Antiretroviral drugs affect glucose or lipid homeostasis either directly, as in the case of protease inhibitors (PIs), or indirectly as with reverse transcriptase inhibitors (RTIs). The PIs directly prevent glucose uptake in 3T3-L1 adipocytes by selectively inhibiting the function of glucose transporter 4 (GLUT-4).[35] This class of antiretroviral drugs also impairs the activation and subsequent build-up of sterol regulatory element-binding protein 1 (SREBP-1) in adipocytes and hepatic cells, leading to dysregulation of adipocyte differentiation and the way glucose and lipids are metabolised.[36] Among the PIs, indinavir (which induces insulin resistance and blocks GLUT-4) is believed to have one of the most potent effects on glucose metabolism – thus, 4 weeks administration to HIV-negative volunteers resulted in insulin resistance.[37,38] However, relatively newer PIs such as lopinavir or atazanavir, often used boosted with ritonavir which also blocks GLUT-4, are believed to have much less effect on glucose and lipid metabolism.[39] Un-boosted lopinavir and ritonavir disturb triglycerides and free fatty acids while un-boosted atazanavir is not implicated.[37] The nucleoside RTIs, including stavudine, zidovudine, and non-nucleoside RTIs like efavirenz (widely used in developing countries) are believed to exert their effects through mitochondrial dysfunction and apoptosis of adipocytes

by inhibition of mitochondrial DNA polymerase-γ and depletion of mitochondrial DNA.[40,41]

Low testosterone and growth hormone deficiency,[42,43] or increased tumour necrosis factor-alpha (TNFα),[44] as seen in PLWH have all been implicated in insulin resistance as well. Lastly, medications such as steroids used in the management of some complications of HIV infection, pentamidine[45] in treating Pneumocystis jiroveci pneumonia, and co-infection with hepatitis C virus (HCV)[46] have also been implicated in dysglycaemia in PLWH. Although, no association was observed in a Swiss cohort,[47] association of diabetes with HCV infection is attributed to insulin resistance, intra-hepatic elevation of TNF levels, and various degrees of liver disease, including hepatic steatosis.[48]

Pathogenesis of hypertension in PLWH

Functional and structural vascular tree changes plus metabolic syndrome/insulin resistance seem to be important in the pathogenesis of hypertension in PLWH. In the general population, narrower retinal arteriolar diameters are associated with the development of hypertension.[49,50] Although atherosclerosis and vasculitis may be assumed from a more general context of HIV-induced inflammation, literature directly linking vascular tree changes in PLWH to hypertension are sparse.[51]

Atherosclerosis, an inflammatory disorder characterised by accumulation of activated macrophages and deposition of oxidised lipids, has been shown to progress faster among PLWH and it occurs even when HIV replication is under control in peripheral blood, and also in those who have never used cART or smoked cigarettes.[52] Also, the massive depletion of gut CD4+ cells early in HIV infection and associated with structural changes in the gut mucosa, allows translocation of bacterial lipopolysaccharide into the blood stream which then activates macrophages.[53]

In addition, excessive sodium and water retention caused by preserved kidney sensitivity to insulin, with high insulin levels produced to overcome insulin resistance, could lead to volume-dependent hypertension.[54]

There is also a possible role for other chronic co-infections like HCV infection in driving the atherosclerotic process, but the independent or relative role HIV or its treatment may play in the pathogenesis of hypertension in such co-infections is less clear.[55] Furthermore, HIV- associated renal impairment either due to immune-complex glomerulonephritis (in populations with an already high prevalence of streptococcal glomerulonephritis) or the use of cART, could lead to development of hypertension.

Conclusions

Frontline healthcare providers should conduct baseline and periodic evaluation for diabetes and hypertension aimed at early detection and prevention. Emphasis must also be placed on promotion of a healthy lifestyle as a preventive measure. Policy planners should advocate and mobilise necessary resources for properly designed surveys to reveal reliable estimates of the burden of diabetes

and hypertension, their risk factors and complications; as PLWH are living longer and experience with cART is increasing. There is now evidence of successful models for the integrated delivery of NCDs and HIV/AIDS services,[15,16] which can make use of the substantial investment in health systems originally meant to tackle only the HIV/AIDS epidemic. These should be piloted and adapted to suit local circumstances with monitoring and evaluation systems built in for continuous improvement.

Author Declaration
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