

## The Effect of HIV and Art on the Development of Hypertension and Type 2 Diabetes Mellitus

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### Abstract

Diabetes mellitus and hypertension [DM] are among the major causes of morbidity and mortality among people living with human immunodeficiency virus [PLHIV]. Diabetes mellitus alone is associated with morbidities that consequently reduce life expectancy and quality of life, and causes demoralising complications inclusive of ischaemic heart disease, stroke, blindness and peripheral vascular disease. Hypertension is an important and treatable cause of cardiovascular morbidity and mortality. It is an independent risk factor for myocardial infarction, chronic kidney disease ischemic and haemorrhagic stroke, heart failure and premature death. HIV infection is associated with morbidities that consequently reduce life expectancy and quality of life. There is a perceived link between HIV infection and DM and hypertension. This is a scoop review of studies on the link between HIV and DM and hypertension, that is, both epidemiologic and biological evidence to date. The literature review shows that the incidence and prevalence of type 2 diabetes [T2DM] is higher among PLHIV on ART compared to the HIV negative population. Being infected by human immunodeficiency virus (HIV) is implied to trigger an inflammatory response that, in turn, results in insulin resistance, a risk for T2DM. HIV is linked to hypertension through alterations in triglycerides, T cells and angiotensin II as well as the aggressive use of ART. The roll out of antiretroviral therapy (ART), as means to combat HIV, has benefits for PLHIV, inclusive of increased survival and living longer; yet older age is associated with hypertension and T2DM. The side effects of ART and long term use of ART are implicated in increasing the risk of T2DM among PLHIV. The co-occurrence of HIV, hypertension and T2DM in developing countries presents an overload to the burden of diseases because these countries are already experiencing high prevalence rates of HIV thereby complicating the health status of the population. Notwithstanding the contrasting research reports on the link between HIV, hypertension and DM hypertension and DM among PLHIV is a cause for concern, and there is a need for more studies, particularly in areas most hit by HIV.

**Keywords:** HIV; Antiretroviral therapy; Diabetes mellitus; Hypertension; People living with HIV; Type 2 diabetes

### Global Burden of HIV Infection

For the past three decades, human immunodeficiency virus (HIV) infection has remained a major global public health concern. Morbidity and mortality rates have continued to negatively impact the life expectancy of many developing and underdeveloped nations. On estimation, about 35 million people live with HIV globally [UNAIDS, 2014]. Of the global HIV prevalence rate, about 67% comes from sub-Saharan African region, and this region accounts for 72% of the world's HIV related mortality [1]. For instance, in Swaziland, one of the sub-Saharan African countries, from the first HIV reported case in 1986, HIV has been rampantly spreading throughout the population [2], to the current prevalence rate of 26% in the reproductive age group of 15-49 years [3]; and among pregnant women receiving antenatal care [ANC], HIV infection has been steadily increasing from 3.9% in 1992 to 41.1% in 2010 [4].

HIV has also had overwhelming negative effects on various countries, on both the economy and development. For instance, in Swaziland life expectancy decreased to 48 years, enlisting it among the lowest in the world; and orphaned and vulnerable children [OVC] were estimated at 104,026 in 2010 [5]. HIV also threatens food security

[6,7] because of the increased demand of agricultural produce explained by the cyclical relationship between HIV and nutrition [8]; yet agricultural activities may be deserted due to ill health. For agro-economy countries, such as Swaziland, poverty is worsened [9], and socio-economic gains reverse [10], putting a question to the long-term survival of such countries [11]. Poverty, unemployment and food security exacerbate the rates of HIV transmission [12], hence the need to combat HIV.

### Response to HIV

In an effort to mitigate HIV and its effects, various countries have embarked on extensive use of antiretroviral [ARV] drugs. Globally, HIV testing and counselling and access to antiretroviral therapy (ART) have been scaled up. Between 2009 and 2011, an increase of 63% in universal ART access has been recorded [13]. Consequently, an estimated 8 million people were on ART in 2011, a steady increase continued and currently more than 9.7 million PLHIV have been initiated on ART [14]. Antiretroviral therapy, sometimes used synonymously with highly active ART (HAART), refers to the use of a combination of three or more antiretroviral drugs [ARVs] to achieve viral suppression while ARVs refer to the actual anti-HIV medicines [15]. To scale up ART access, the World Health Organisation [WHO] has been modifying and improving ART guidelines. Initially, the guidelines provided guidance for HIV infected adults and for

prevention of mother to child transmission [PMTCT] of HIV [16]. In 2006, the guidelines were updated to incorporate a concept of public health [17]. In 2010, further modifications to include the aspect of CD4 count, <200 cells/mm<sup>3</sup>, at which ART should be initiated and was later changed to a CD4 count of <350 cells/mm<sup>3</sup>. Recently, in 2013, the CD4 count of ART initiation was changed to 500 CD4 cells/mm<sup>3</sup> [18]. Recently, a new program, 'test and start' [19], has been initiated in many countries, whereby one's CD4 cell count is no longer used as a parameter to initiate one on ART, but their HIV positive status. The aim is to enroll as many PLHIV as possible into ART. In Swaziland, this program was initiated in October 2016 and is implemented in all ART initiating health facilities [20].

These changes have and still are profoundly increasing the proportion of PLHIV on ART. For instance, in Swaziland by December, 2010, about 78 919 of the 220 000 HIV infected persons were initiated on ART, of whom 49 371 were women [21], and now Swaziland is among the Sub-Saharan African countries with 80% ART coverage [22], and 83% among pregnant women [23]. ART has also vividly reduced HIV related morbidities and mortalities [24], and life expectancy among people living with HIV [PLHIV] has increased [25].

HIV care has also been modified to cover opportunistic infections, particularly tuberculosis [TB]. Consequently, much effort has been focused in integrating TB and HIV care for PLHIV, with success. This implies that various countries are heading towards a favourable position towards eliminating Acquired Immune Deficiency Syndrome [AIDS] and reducing new HIV infections. PLHIV are therefore likely to live longer albeit they are HIV positive. The rollout of ART increases survival of PLHIV which is in line with the 90/90/90 Joint United Nations Program on HIV/AIDS [UNAIDS] targets for the end of AIDS campaign [25]. However, as the number of people on ART increases, the age of PLHIV also increases, raising concerns such as the coexistence of HIV with non-communicable diseases [NCDs]. This suggests the importance of monitoring the incidence of NCDs such as diabetes mellitus, hypertension and other cardiovascular related conditions in addition to access, adherence and retention to treatment among PLHIV.

Albeit there is progress in combating HIV and integrating TB and HIV care, there has been an increment, particularly in developing countries, in the incidence of non-communicable diseases including diabetes mellitus, high blood pressure and cardiovascular diseases. In the same vein, diseases such as peripheral neuropathy, mental disorders, type 2 diabetes mellitus [T2DM], hepatitis, kidney disease, lung disease, gastrointestinal disease, AIDS-related cancers and neurological diseases have become non-communicable diseases of concern in HIV infection and rollout of ART [26].

## Diabetes Mellitus

Diabetes mellitus [DM] is one of the most important non-communicable diseases of public health concern in both developed and developing countries and is apparently dynamic. The global prevalence of diabetes in 2013 was 382 million people and is projected to increase to 592 million in 2035 [27]. These projections of DM are likely to intensify in the developing world secondary to, in part, HIV and ART, and the noticeable revolution of lifestyles in these countries [28].

DM is defined as a collection of disorders relating to metabolism that manifest by increased levels of glucose in the blood, subsequent to malfunction in either insulin secretion or action [29]. These metabolic

disorders are often a consequence of autoimmune-mediated destruction of beta cells in the pancreas thereby leading to decreased insulin secretion [30] or can be secondary to abnormalities in the action of insulin [type 2 diabetes mellitus]. Of all DM cases globally, T2DM accounts for about 90%, and the remaining 10% is attributable to type 1 diabetes mellitus [31]. The mechanisms through which type 2 diabetes mellitus [T2DM] develops relate to insulin resistance, adipose tissue [entails free fatty acids], tumour necrotic factor-alpha [TNF- $\alpha$ ], Peroxisome proliferator activated receptor gamma [PPAR $\gamma$ ], interleukins, fuel oxidation, insulin secretion dysfunction, pancreas beta cells dysfunction and glucotoxicity [32]. In line with WHO standards, DM is diagnosed when a person has fasting plasma glucose [FPG] of  $\geq 7.0$  mmol/L glucose and a fasting 2-hour plasma glucose following administration of 75 g oral glucose  $\geq 11.1$  mmol/L [WHO, 2006]. According to these standards, DM should be differentiated from impaired glucose intolerance [IGT], which is when a person has FPG ranges of  $\geq 7.8$  to  $<11.1$  mmol/L measured 2 hours post ingestion of 75 g oral glucose [WHO, 2006]. The focus of this review is T2DM and hypertension.

DM alone is associated with morbidities that consequently reduce life expectancy and quality of life. It causes demoralising complications inclusive of ischaemic heart disease, stroke, blindness as well as peripheral vascular disease [33]. Several studies identified DM risk factors as heredity, diet and level physical activity [Currier et al. 2008; Ebrahim et al. 2013b; Gillett et al. 2012], but there is growing evidence that there is link between HIV and T2DM [34-38]. The molecular events resulting from HIV infection and exposure to ART are similar to those that lead to diabetes [39], hence the link between HIV and the risk for diabetes.

## Hypertension

Hypertension is a global issue and has led the World Health Organization to declare that suboptimal blood pressure is the leading risk for death in women and the second leading risk for death in men in developed countries [40,41]. Hypertension refers to an elevated blood pressure. It is an important and treatable cause of cardiovascular morbidity and mortality. Hypertension is an independent risk factor for myocardial infarction, chronic kidney disease, ischemic and haemorrhagic stroke, heart failure and premature death. Pharmacologic treatment should be initiated when the systolic pressure is 140 mm Hg or higher, or when the diastolic pressure is 90 mm Hg or higher. The target systolic pressure is less than 140 mm Hg, and the target diastolic pressure is less than 90 mm Hg [42]. Although the World Health Organization has recommended that treatment and control of hypertension is a global health priority, there is no consensus on how this should be accomplished [43]. There is substantial evidence that physicians frequently do not follow hypertension management guidelines and that current physician practice patterns represent a major barrier to the treatment and control of hypertension [44-47].

## HIV, diabetes mellitus and hypertension

The prevalence of DM and hypertension among PLHIV makes these conditions non-communicable disease of concern. DM prevalence in HIV infected people ranges from 2-14% [48]. The co-occurrence of DM and hypertension in HIV is becoming a threat to public health, especially in developing countries, lately. Back in 2000 and 2003, the correlation between HIV and DM was negative: [r=-0.434, p<0.001] and [r=-0.281, p=0.02], respectively [49,50]. However, a persistent

increase in the prevalence of HIV and DM has since been observed as of 2007 [ $r=0.346$ ,  $p=0.004$ ] and 2010 [ $r=0.440$ ,  $p<0.001$ ] [51,52].

The above findings support that DM and hypertension are emerging NCDs in HIV infection and demand attention from countries with high prevalence rates of HIV infection. The intensification of DM and hypertension in HIV infection contributes to the transition of HIV from being an acute condition to a chronic condition and implies a link between these conditions.

Various studies have reported the link between HIV, hypertension and T2DM to be inherent in HIV infection itself, adverse effects of ART and long-term use of ART, in addition to lifestyle, genetics and aging [53]; but there is contrasting evidence whether HIV infection itself predisposes one to T2DM and hypertension or not.

### HIV and T2DM

The major implicated way through which HIV predisposes one to T2DM is through the inflammatory response process occurring during HIV infection. Infection with HIV results in increased inflammatory markers. Inflammatory markers related to HIV infection have been implicated as causally associated to premature onset of chronic diseases [54], and T2DM and hypertension are some of the chronic diseases predicted by inflammatory markers in HIV infection [55]. The commonly identified inflammatory markers in HIV infection include interleukin-6 [IL-6], and sensitivity C-reactive protein [hsCRP] and have been reported to be higher among those who developed T2DM compared to those who did not: 3.45 versus 2.50 pg/mL for IL-6 and 4.91 versus 3.29  $\mu$ g/mL for hsCRP, both  $p<0.001$  (Dooko, 2014). Individuals infected with HIV are also reported to have significantly higher levels of d-dimer and cystatin C inflammatory biomarkers compared to those not infected [56,57].

More studies have alluded to that HIV infection predispose one to diabetes. There is observed higher incidence of diabetes in HIV infected people compared to the non-HIV infected [58]. About half of HIV infected people can develop diabetes [59], and diabetes can be diagnosed even among patients newly infected with HIV, not on ART [60,61].

On another note, other studies have provided contrasting evidence. Some studies have reported a higher prevalence of diabetes in the general population compared to HIV infected people [62] while other studies reported that there are other risk factors, other than HIV infection alone, that lead to diabetes. These include being pre-diabetic at the time of HIV infection [63], having other HIV related opportunistic diseases such as TB [64], and having elevated levels of glycated haemoglobin [A1C] (Tien et al. 2012); hence HIV alone is argued to be associated with a lower risk of DM at baseline [65]. These studies hold that other factors other than HIV infection alone influence the development of diabetes among PLHIV [66].

Therefore, the direct influence of HIV on diabetes remains unclear. It is argued that other factors relating to HIV underlie the likelihood for DM to develop, yet the extent to which traditional factors may influence the development of DM in HIV infected and uninfected persons remains controversial and demands more studies to be conducted, especially in countries with a high prevalence of HIV. The above mentioned studies also suggest that TB could be a confounder of diabetes hence more studies that will determine the prevalence of DM stratified by TB infection are needed, particularly in the African context where HIV/TB co-morbidity is common, but such studies are scarce. On another note, there are few studies in the sub Saharan

region reporting on the prevalence of DM in HIV infected patients yet this region is hard hit by HIV. Another constraint of most of the aforementioned studies was lack of national representativeness; hence more studies looking at the prevalence of DM among HIV infected persons are needed, otherwise it remains questionable that HIV infection directly influences the development of diabetes, and those countries with high HIV prevalence rates need a model of care pertaining diabetes among PLHIV.

### Diabetes mellitus and ART

Antiretroviral therapy has been implicated in the development of diabetes among PLHIV. Diabetes incidence and prevalence has been reported higher among PLHIV on ART compared to the HIV negative population [67]. Studies conducted in Africa also reported an increase in the prevalence of diabetes among PLHIV and on ART for years [68]. Antiretroviral therapy and longer exposure to ART are associated with diabetes related metabolic syndrome [69]. In fact, diabetes prevalence is 5-9 fold higher in PLHIV with metabolic syndrome [70].

Generally, the adverse effects of ART and long-term use of ART are implied to trigger body mechanisms that lead to development of T2DM. Antiretroviral therapy is implicated in the development of metabolic changes related to fat distribution and glucose homeostasis [71]. Introduction of ART to the body leads to increased levels of TNF- $\alpha$ , which, in turn, impairs metabolism of fatty acids and lipid oxidation, resulting in suppressed lipolysis [72]. This, in turn, results in altered fat distribution, and subsequent changes in lipid profile, evident in an observed increase in the levels of triglycerides and low density lipoprotein [LDL] cholesterol, and a decrease in high density lipoprotein [HDL] cholesterol [73].

Since early 19th century, increased triglycerides [hypertriglyceridemia] have been associated with poor virological control [74], implying a subsequent difficulty for the body to control viral infection with HIV; yet this process leads to further increased levels of TNF- $\alpha$  [75-77]. This suggests that the interaction between TNF- $\alpha$ , hypertriglyceridemia, and poor viral infection control is cyclical. Hypertriglyceridemia ultimately results in insulin resistance [78], a risk factor for T2DM. Insulin resistance develops as a result of ART binding to the insulin sensitive glucose transporter [GLUT 4] causing blockage [79].

Antiretroviral therapies further inhibits differentiation of adipocytes and hinder polymerase- $\gamma$ , with a subsequent mitochondria dysfunction [80]. Protein inhibitors [PI], which are the main cause of adipocytes differentiation inhibition, alter the expression of sterol regulatory element-binding protein-1 [SREB-1] and peroxisome proliferator-activated receptor- $\gamma$  [PPAR- $\gamma$ ], which are inevitably necessary for differentiation of adipocytes [81]. Hindrance of polymerase- $\gamma$  coupled with drain of mitochondrial deoxy nucleic acid [DNA], termed mitochondrial toxicity, both caused by nuclear reverse transcriptase inhibitors [NRTIs], are also implicated in the development of diabetes among PLHIV on ART [82]. Both mitochondria dysfunction and adipogenesis result in insulin resistance and subsequent development of diabetes as summarised in Figure1.

Protein inhibitors and NNRTI are also implicated in causing lipodystrophy and dyslipidaemia [83]. Lipodystrophy, a clinical manifestations of metabolic syndrome, is a complex syndrome thought to be a secondary effect of HIV infection, direct drug-induced toxicities and the indirect effects of lipid metabolism changes [84]. Dyslipidaemia, a metabolic disorder, is characterised by



hypertriglyceridaemia, hypercholesterolemia and low levels of high density lipoprotein [85], and results from erroneous metabolism of lipoprotein [86]. Hypertriglyceridaemia has been found to be associated with acute pancreatitis [87], a potential for altered function of the beta cells in the pancreas and subsequent development of diabetes.

Dyslipidaemia and lipodystrophy have been reported to be severe and prevalent with ART use [88]. Protein inhibitors such as ritonavir have been reported to cause a striking increase of triglycerides in less than six months post ART initiation [89]. Some studies have reported some ARVs that are associated with dysfunctional metabolism: nevirapine, stavudine, lamivudine [90], efavirenz [91] indinavir, saquinavir, didanosine [92] and zidovudine [93]; yet some studies reported that both hypertriglyceridaemia and hypercholesterolemia have been observed among HIV positive patients on ART regardless of regime [94]. This implies that all ART regimes may not completely spare HIV infected patients from metabolic disorders and the subsequent risk of diabetes. In fact, Wohl concluded that the antiretroviral drug that causes the most severe accumulation of visceral fat is unknown. Therefore, even with reviewed ART regimes, the need to monitor patients on ART for development of diabetes cannot be over emphasised, particularly in the era of universal ART access.

Albeit there are other factors associated with development of diabetes such as gender – being male [95], obesity, poor dietary habits, heredity and physical inactivity [96], and age [97], the evidence that ART is associated to diabetes cannot be refuted.

Even though plausible similarities have been reported in the hypothesised link between DM, HIV and ART, certain controversies exist. Some studies have reported higher prevalence of diabetes among women [98] while others among men [99] infected with HIV. Contrary to the high diabetes prevalence among PLHIV [100], some studies reported a lower prevalence among the HIV positive population compared to HIV negative population. These controversies warrant more studies to be undertaken [101].

## HIV, ART and hypertension

HIV infection is implicated in the development of hypertension. Presently, the exact mechanism underlying the association between HIV infection and many aging-related chronic diseases remains unknown [102]. HIV infection without ART initiation is associated with significant changes in lipids, hepatic and hematologic biomarkers [ $p < 0.01$ ]. Specifically, triglycerides increase [103]. These changes occur without significant changes in BMI, and can happen relatively quickly, that is, 1.8 years, with moderate reduction in median CD4 cell count [104]. This evidence does not only suggest that HIV infection prior to ART initiation is associated with changes in individual risk factors [e.g., serum lipids] but more importantly, that the changes in multiple biomarkers across several organ systems may be indicative of a pro-inflammatory response [105]. For instance, serum triglycerides, which increase following infection, have been correlated with interferon  $\alpha$ , a pro-inflammatory cytokine [106] related to chronic cardiovascular conditions including hypertension. If the changes in these biomarkers associated with HIV infection are indicative of an underlying pro-inflammatory state, it is possible that even with successful ART, the excess risk of end organ disease that is associated with HIV infection may not be completely eliminated. For instance, some studies found that HIV infection followed by ART initiation and HIV-1 RNA of less than 500 copies/mL does not reverse alteration in triglycerides and

LDL cholesterol to pre-HIV infection levels [107] hence the risk for hypertension still remains.

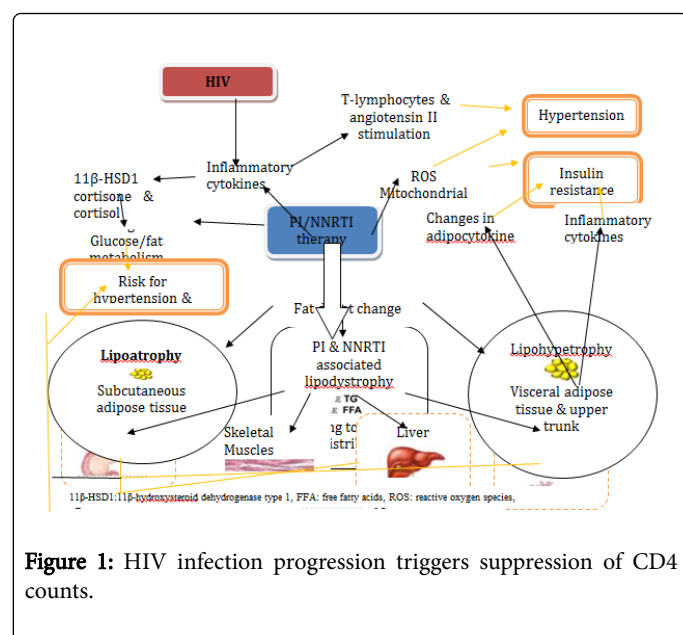
Another mechanism through which HIV infection triggers hypertension is through the T lymphocytes response to HIV infection, and the interaction between T lymphocytes angiotensin II. Angiotensin II is a hormone which is an important mediator of hypertension. It increases thirst, causes vasoconstriction, promotes salt retention by the kidney, and enhances the release of catecholamines from nerves and the adrenal gland [108]. Angiotensin II also directly promotes inflammation and the development of atherosclerosis [109]. HIV infection triggers the body proliferation of T lymphocytes in the acute phase, and Angiotensin II stimulates T cell proliferation [110]. T lymphocytes contain a functional Nox-based nicotinamide adenosine dinucleotide phosphate [NADPH] oxidases [111] and an AT1 receptor [112]. These are multi-sub-unit enzymes that are similar to neutrophil oxidases found in vascular cells, kidneys, and central nervous system [113] that are responsible for vasoconstriction and salt retention in the kidneys. Angiotensin II can activate these enzymes, and the O<sub>2</sub><sup>-</sup> that is subsequently produced can react with the endogenous vasodilator nitric oxide [NO] at diffusion-limited rates, thereby promoting vasoconstriction [114]. These Nox enzymes also produce reactive oxygen species [ROS] which have been implicated in several models of experimental hypertension [23]. These processes increase systemic vascular resistance and elevate blood pressure.

Recent studies provided further evidence that certain T cells are essential for the development of hypertension [10]. The specific subsets of T cells that are important in hypertension are unknown. Traditionally, T helper cells are thought to differentiate into distinct subsets as Th1 and Th2 with different functions and patterns of cytokine secretion [6]. An imbalance in Th1/Th2 subsets is implicated in resistance and susceptibility to infection [2], the pathogenesis of autoimmune diseases including diabetes mellitus [8], the development of atherosclerosis [86], and hypertensive kidney disease [6]. More evidence suggests that T helper cells have a subset that produces a unique cytokine, IL-17 [99] which has been implicated in the pathogenesis of many autoimmune and inflammatory diseases, and evidence supports that IL-17 has a role in cardiovascular diseases [56]. Importantly, IL-17 synergizes with other cytokines, such as TNF- $\alpha$ , to modulate inflammatory responses [52], and TNF- $\alpha$  plays a critical role in angiotensin II- induced hypertension, [110] and contribute to the hypertensive phenotype [6].

On another note, HIV infection progression triggers suppression of CD4 counts, and those patients have a low incidence of hypertension [6]. Conversely, the aggressive use of ART to achieve viral suppression also leads to increase in blood pressure through changes in fat metabolism and distribution [22]. This is summarised in Figure 1.

Collectively, these studies suggest that adaptive immunity and ART contributes to the development of hypertension and diabetes, and the mechanisms that take place can lead to a concurrent development of both. Albeit there is plausible research evidence that HIV and ART can lead to hypertension, most of these studies were experimental and in-vivo. There are limited studies comparing the incidence and prevalence of hypertension between PLHIV and the negative population. There is limited evidence to firmly rule out if hypertension in PLHIV is due to other risk factors other than HIV infection and ART alone. Of note, most studies on the link between T2DM, hypertension and HIV come from high income countries, and those findings cannot be used to infer to the settings in sub-Saharan Africa because of the potential difference in the two settings [113]. Data that feature developing countries

predominately focus on Latin America, Asian, East and West African countries. Thus far, data reported on sub-Saharan African countries covers few countries to create a clear picture of the burden of diabetes and hypertension in this part of the world, implying a gap in studies focusing on DM and hypertension among PLHIV in sub-Sahara Africa; hence there is a need for data from sub-Saharan Africa to quantify the burden of DM and hypertension among PLHIV as well as quantification of all the factors associated with the risk of hypertension and T2DM in this group of patients.



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