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Treatment of Acquired Diabetes Mellitus in People Living with Human Immunodeficiency Virus: A Review

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Abstract

A higher incidence of new-onset diabetes mellitus (NOD) has been consistently observed in people living with HIV (PLHIV) after receiving highly active antiretroviral therapy (HAART). Most NOD in PLHIV occur after use of HAART and both insulin resistance and impaired β-cell insulin secretion have been found to underlie the disturbed glucose metabolism. The use of glycated hemoglobin (HbA1c) to diagnose or screen DM has been noted to significantly underestimate glycemia status and to have the least yield when compared to using standard oral glucose tolerance test (OGTT) or fasting glucose levels, and should be interpreted with caution. Low hemoglobin values, or hemolysis that causes shortened erythrocyte lifespan have been associated with lower HbA1c values. For better yield of making earlier diagnosis, the conjunction of HbA1c with either fasting plasma glucose levels or standard OGTT is thus recommended in HIV-infected patients. Treatment of DM according to the contemporary guidelines is practical but caution must be taken when there could exist HAART-associated mitochondrial toxicity which may result in buildup of lactic acid, in which case metformin use is contraindicated. HAART-induced hepatotoxicity should be evaluated before prescription of thiazolidinedione. The DPP4 inhibitors have a safe profile regarding immune or virological status, but the dose needs to be reduced when co-administered with a CYP3A4/5 inhibitor (such as protease inhibitors) due to altered plasma concentration profile of the gliptins. With increasing incidence of DM among PLHIV receiving HAART, clinicians are encouraged to keep high profile of clinical vigilance to ensure an appropriate management for patients who may suffer from a new disease while having been treated for an existing one. An understanding of the underlying pathophysiological processes of glucose dysmetabolism linked to antiretroviral therapy will help clinicians treat their patients in a more competent manner. (J Intern Med Taiwan 2021; 32: 264-280)

Key Words: DM, Highly active anti-retroviral therapy, HIV infection

Introduction

With the ever-advancing understanding of the many faces of human immunodeficiency virus (HIV) and the clinical features of consequent acquired immunodeficiency syndrome (AIDS) it causes in human beings, this once devastating disorder that leads to breakdown of the immune system and high

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mortality from opportunistic infections in these immunocompromised individuals for decades has now gradually transformed into a disease that is chronically controllable with significantly reduced mortality and prolonged life span, mainly thanks to the development and application of the highly active anti-retroviral therapy (HAART), which works effectively in collaboration with other preventive and monitoring strategies deployed in the HIV care continuum[1,2]. However, with the expanded life span earned from reduced life-threatening infections in these HIV-infected individuals came the increased incidence of non-communicable diseases that mirror those in the currently aging population, and diabetes mellitus (DM) is one that emerges as a prominent feature and deserves high profile of clinical attention because of the significant prevalence of co-morbidities and mortality associated. This changing face of HIV infection has been observed not only in countries or regions with high HIV infection prevalence, but also in Taiwan[3-7].

This narrative review article starts with giving shape to the facts on epidemiology of DM in people living with HIV (PLHIV), followed by the discussion on pathophysiological processes leading to the development and progression of glucose dysregulation in subjects treated with HAART, and will end with contemporary consensus regarding the diagnosis of DM and use of anti-diabetic agents based on certain specific considerations in this group of patients who are receiving multiple medicines (polypharmacy).

Abbreviations:

ART: anti-retroviral therapy; **DM:** diabetes mellitus; **HAART:** highly active anti-retroviral therapy; **HOMA-β:** homeostasis model assessment for β-cell function; **HOMA-IR:** homeostasis model assessment for insulin resistance; **IR:** insulin resistance; **INSTI:** integrase strand transfer inhibitor (e.g. dolutegravir, elvitegravir, raltegravir); **NRTI:** nucleoside reverse transcriptase inhibitor (e.g. didanosine, emtricitabine, lamivudine, tenofovir); **NNRTI:** non-nucleoside reverse transcriptase inhibitor (e.g. efavirenz); **PI:** protease inhibitor (e.g. atazanavir, darunavir, indinavir, lopinavir, ritonavir).

Incidence of diabetes mellitus in people living with HIV (PLHIV)

In a prospective research carried out in a cohort of veterans in the US[8], participants that were HIV-infected showed a baseline demographic features of younger age, a significantly lower body mass index (BMI), but more likely to be male, having hepatitis C (HCV) co-infection, and black race when compared with the HIV-uninfected counterpart. The prevalence of DM at study entry was lower in the HIV-infected subjects compared with those uninfected (14.9 vs. 21.4%, $p < 0.0001$, Odds ratio (OR) 0.84, 95% Confidence interval (CI) 0.72-0.97). No association between baseline DM status and HIV RNA levels was found. HIV-infected or not, the prevalence of DM at baseline shared the common risk factors but the OR associated with increasing age, minority race and BMI were greater among those HIV-infected subjects. The lower prevalence of DM observed in the HIV-infected group was driven mostly by the difference in those with lowest BMI, suggesting that an improved health status might play a role leading to a higher risk of DM, and this was further strengthened by the observation that there was an increased risk of DM in those with a higher CD4+ lymphocyte counts, an indicator of better health status. The authors also found a higher risk of DM in HIV-infected subjects when there was HCV co-infection (a finding not observed in HIV-uninfected controls) and when nucleoside and non-nucleoside reverse transcriptase inhibitor (NRTI and NNRTI, respectively) therapies were in use. A conclusion was drawn from this research that HIV infection per se had lower risk of DM, while increase in age, presence of HCV co-infection and

higher BMI impacted more upon the risk. Long term ART played another significant role in the development of incident DM when the cumulative exposure duration to these medications was longer than one year, a cutoff time marker used in this analysis, compared to that of less than one year.

A lower or similar incidence of DM in HIV-infected individuals compared to non-infected counterpart was also observed in other studies. In the "Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study"[9], the DM incidence rate in those HIV-infected females not on HAART was found to be 1.53/100 person-years (PY), and the corresponding figures of 2.50/100 PY in those reporting on HAART containing a protease inhibitor (PI) and 2.89/100 PY in those reporting on non-PI-containing HAART, respectively, did not show statistical difference when compared to the HIV-uninfected women (1.96/100 PY). However, further analysis among the HIV-infected population itself who had received NRTI therapy showed that there was a higher incidence of DM compared to those who had not, with a relative hazard ratio (HR) of 1.81 [95% CI 0.83–3.93] in those with > 0 to 3 years of exposure and a HR further up to 2.64 (95% CI 1.11–6.32) in those with > 3 years of exposure, a finding indicating an association between higher risk of new-onset diabetes (NOD) and longer exposure to this treatment regimen. Another cross-sectional analysis based on a community survey (the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)) had found that in those ART-naïve HIV-infected subjects, when compared with the general population in a nation-wide general health status survey program in the US, the prevalence of DM was lower among the CPCRA participants than the NHANES participants (3.3% vs. 4.8%; $p < 0.01$)[10].

On the other hand, other studies differed in findings. In the Multicenter AIDS Cohort Study (MACS) carried out in male subjects, despite a lower BMI and younger age in the HIV-infected group, the occurrence of DM was higher than the non-infected counterpart after adjustment of the traditional risk factors for incident DM at a prevalence ratio of 2.21 (95% CI 1.12-4.38) in those who were not treated with HAART, and this figure more than doubled to 4.64 (95% CI 3.03-7.10) in those on HAART[11]. In a more recent nation-wide survey in the US (NHANES between 2009 and 2010) using data derived from the HIV-infected subjects attending the Medical Monitor Project (MMP), from which the participants were receiving medical care, the unadjusted prevalence of DM among HIV-infected adults was 10.3% (9.1% to 11.5%), which was higher compared with the general US adult population in that NHANES survey at 8.3% (7.2% to 9.4%), from which derived a computed prevalence difference of 3.8% higher in the HIV-infected groups. Factors independently associated with prevalence of DM among HIV-infected participants were increasing age, obesity, increasing time since HIV diagnosis, and geometric mean of CD4 counts. Of note, higher DM prevalence at younger ages and in the absence of obesity was found in HIV-infected adults when compared to general population in this survey[12].

In South Africa where HIV infection has high prevalence, a community-based survey was conducted by first checking fasting glucose as screening and followed by standard 75-g oral glucose tolerance test (OGTT) for confirmation purpose. The authors found the prevalence of dysglycemia (putting together DM, impaired glucose tolerance, and impaired fasting glucose) increased progressively in the following orders of study groups stratified: HIV-uninfected (18%), ART-naive HIV-infected (21.6%), the first-line ART (NNRTI plus dual NRTIs) (26.0%), and the second-line ART [lopinavir/ritonavir-boosted (both PIs) plus dual NRTIs used in this survey] group (37.0%). The likelihood risk for dysglycemia increased significantly ($p < 0.001$) in the HIV-infected participants

when compared to the HIV-uninfected counterpart. Among the HIV-infected groups, a similar likelihood existed between ART-naive (OR 2.31, 95% CI 1.65-3.24) and first-line ART (OR 2.47, 95% CI 1.80-3.38) participants, but went higher in the second-line ART group (OR 4.10, 95% CI 2.54-6.61)[13].

In a longitudinal observation study on the incident DM after HAART initiation among a cohort of PLHIV in the Asia-Pacific region, 7% of the participants developed DM, with an incidence rate of 1.08 per 100 PY (1.08/100 PY) (95% CI 0.9 to 1.3), after a median follow-up time of 5.9 years (interquartile range: 2.8 to 8.9 years). Co-infection of HCV has shown a tendency toward higher incidence rate at 1.18/100 PY, when compared to 1.05/100 PY in HCV-negative participants. Risks of DM development in addition to ART included older age, higher BMI and high blood pressure. The conclusion drawn by the authors highlights the importance of monitoring and routine screening for non-communicable diseases, including DM, as PLHIV age, especially in those on long-term HAART[14].

In a prospective multicenter cohort study carried out in non-pregnant women with HIV infection, there existed a nearly 3-fold higher incidence of NOD among PI users compared to those who had received NRTI and those not receiving ART therapy (2.8/100 PY vs. 1.2/100 PY, $p = 0.01$ for comparison between PI users and the NRTI users). Age and BMI were again noted to be independent risk factors in this female population[15].

A retrospective case-control study carried out in a tertiary referral medical center in Taiwan had found the incidence of DM in HIV-infected individuals who were receiving HAART to be 1.31 /100 PY during a follow-up period spanning from 1993 to 2006. The risk factors for incident DM included a family history of DM and current use of PIs[16]. Furthermore, a nationwide population-based study in Taiwan using the National Health Insurance Research Database available between year 2000 and 2010 reported that, in HIV-infected patients, those receiving HAART had a significantly higher 10-year cumulative incidence rate of DM compared to those not receiving HAART (7.16% vs. 2.24%, $p < 0.001$). Additional to receiving HAART, the presence of hypertension, gouty arthritis, and co-infection with HCV was also significantly associated with increased risk of DM[7].

Will incident DM be reduced in HIV-HCV-co-infected patients after eradication of HCV?

Co-infection of HIV and HCV has been noted in most of the epidemiological studies in HIV-infected subjects. The overlapping pathways of transmission between HIV and HCV may contribute to this phenomenon. The negative sides of HIV infection include increase in HCV replication, augmented HCV-induced hepatic inflammation, and increase in hepatocyte apoptosis[17]. On the other hand, HCV infection alone has been linked to higher incidence of type 2 DM (T2DM) than general population or hepatitis B-infected subjects[18]. A recent meta-analysis has reported that, from data derived from a total of 14,765 study participants in 40 articles analyzed, the pooled prevalence of T2DM among HCV-infected patients was 19.67%, a figure that is much higher than the general population at around 10%. Subgroup analysis in regional prevalence showed a figure of 20.73% in Asia[19] . The major pathophysiology underlying HCV-associated T2DM was insulin resistance in the presence of HCV infection, while no β-cell function defect has been identified in clinical studies. In a sophisticated study applying euglycemic hyper-insulinemic clamp method (the gold-standard method of studying *in vivo* insulin sensitivity in various insulin-sensitive tissues, including skeletal muscles, liver, and adipose tissue) carried out in 14 patients with biopsy-proven chronic hepatitis C, there were significant reduction in total glucose disposal due to impaired glucose oxidation, higher

endogenous glucose production from the liver, and less suppression of lipid oxidation in the presence of high concentrations of insulin, together of which indicate that HCV infection *per se* is associated with peripheral and hepatic insulin resistance. Enhanced hepatic expression of inflammatory cytokines/mediators could be involved in the defective glucose regulation[20]. If glucose metabolism is altered by the presence of HCV, hypothesis would form that the eradication of HCV would be expected to result in the improvement of glucose homeostasis, and even a decrease in incident T2DM. In 12 lean HCV-infected patients without significant fibrosis of the liver who were treated with combination therapy composed of direct-acting antiviral (DAA) regimen sofosbuvir/ledipasvir and ribavirin, an euglycemic hyper-insulinemic clamp was applied before and 6 weeks after the treatment period to assess the impact of treatment on extrahepatic effects regarding insulin sensitivity. The results had shown that, in those patients who achieved complete viral suppression after 6 weeks of therapy, there was a significant improvement of insulin sensitivity in skeletal muscles compared to the baseline values (13.1%, $p = 0.003$)[21]. Meta-analysis on published research works has shown that, after interferon(INF)-based antiviral therapy (ribavirin), patients who achieved sustained virologic response (SVR) had a significantly more reduction in HOMA-IR and HOMA-β, as compared to the non-SVR counterpart[22]. A simultaneous reduction in HOMA-β may indicate amelioration in insulin resistance status, which in turn leads to a less demand on the insulin secretion from pancreatic β-cells. Furthermore, improvement in glycemic control after SVR has been reported in both prospective and retrospective clinical studies and the improvement is associated with status of SVR[23-26]. From a longitudinal follow-up study carried out in Japan in a cohort of 2,842 HCV-infected subjects, a total of 143 participants were identified to have developed incident T2DM during the study period spanning 15 years. The cumulative development rate of DM was 3.6%, 8.0%, and 17.0% at 5, 10, and 15 years, respectively. Multivariate hazard analysis revealed that DM development after the termination of INF therapy was associated with advanced histological staging, non-sustained virological response, history of pre-diabetes, and age > 50 years. The authors concluded that achievement of SVR causes a two-thirds reduction in the risk of incident T2DM in HCV-infected patients treated with INF[27]. Another more recent report also concluded with the similar findings of reduced incident DM after SVR in HCV has been achieved[28].

In HIV/HCV-co-infected patients, evidences derived from follow-up clinical trial also found reduced incident DM after eradication of HCV. In a longitudinal study carried out in Spain in which non-liver- and non-AIDS-related events and mortality in a cohort of HIV/HCV-co-infected patients treated with INF and ribavirin between 2000 and 2008 were assessed. After a median five-year follow-up, a significant reduction in the hazard of incident DM (adjusted subhazard ratio 0.57 [95% CI, 0.35-0.93] $p = 0.024$) was observed among those 592 (36% of the total cohort of 1,625 patients recruited) participants who had a sustained SVR[29].

Mechanisms of glucose dysregulation after use of ART

In 1997, the Federal Drug Administration (FDA) of the US announced that there existed a relationship between NOD in HIV-infected patients treated with PIs[30]. Most epidemiological studies on the prevalence of DM among HIV-infected patients, whether lower or higher than the figures in the background general population, have shown higher incidence rate after the use of ART when compared to treatment-naïve time period. Understanding of the underlying pathophysiological processes linked to impaired glucose homeostasis with use of ART derived mostly from studies in earlier years when

the endemic of HIV infection and various therapies have been on the rise. A large-scale study of a total number of 849 HIV-infected participants (443 on ART and 406 ART-naive) carried out in the Sub-Saharan Africa, the region of which accounts for 67% of HIV infection worldwide, investigated several parameters relevant to glucose metabolism after the use of NNRTI-based ART[31]. A standard 75-g OGTT was done and, with the blood glucose and insulin concentrations derived from the test, various assessment including insulinogenic index (IGI) [the ratio of the change in insulin to the change in glucose from 0 to 30 min ($\Delta Insulin_{0-30}/\Delta Glucose_{0-30}$) after glucose ingestion], the HOMA-β (20 x fasting insulin/fasting glucose - 3.5), and the oral disposition index (D_o, $\Delta Insulin_{0-30}/\Delta Glucose_{0-30}$ x 1/ fasting insulin) were applied to assess the pancreatic β-cell insulin secretion ability in response to the ambient insulin resistance status. Insulin sensitivity was assessed by HOMA-IR (fasting glucose x fasting insulin/22.5)[32]. The results showed that in ART-users, those with dysglycemia were more insulin resistant, had reduced β-cell function and IGI, and had a lower Do compared to the normoglycemic group. Similar findings were noted among ART-naïve subjects with different glycemic status. The authors also found that for patients with dysglycemia from OGTT test, those on ART had more prominent central obesity (higher waist circumferences, WC) but a wasting in peripheral fat, suggesting a link between the occurrence of dysglycemia and increased visceral adiposity as well as wasting at peripheral sites (a mixed type lipodystrophy). In contrast, in the ART-naive patients, those with dysglycemia were overweight (higher BMI), with more visceral and superficial abdominal adiposity (greater WC and abdominal skinfold thickness) but no peripheral wasting. Older age, male gender, higher CD4 count, and use of efavirenz were significant risk factors for development of dysglycemia after multivariate analysis. The higher BMI and greater WC were most likely accounted for by the subjects with higher CD4 counts, possible indicators of less immunosuppression and better health status in this group of patients (as patients with lower CD4 counts often have more advanced HIV infection). A significant association between the use of efavirenz (in patients who had only ever received efavirenz as the third drug) and dysglycemia was noted in this research and the authors considered the higher BMI and greater WC contributed by this NNRTI cannot be excluded. In another research by using the euglycemic hyperinsulinemic clamp technique, an acute effect of single dose of indinavir administered to healthy HIV-uninfected male volunteers demonstrated significant suppression of insulin-mediated total and non-oxidative glucose disposal rate, findings similar to insulin resistance seen in T2DM patients in the general population[33,34]. Further studies have revealed the blocking by these agents of transportation of glucotransporter-4 at the subcellular level in *in vitro* studies in cultured 3T3-L1 adipocytes, another evidence of insulin resistance that hinders the entrance of glucose into the cells[35,36].

PIs had been found to not only cause insulin resistance but also impair insulin secretion function of β-cells. By using the minimal model analysis (a method that can assess at the same time the acute β-cell insulin secretion response to hyperglycemia stimulation as well as general insulin sensitivity), the use of indinavir in HIV-infected patients who had no DM at baseline was found to decrease insulin sensitivity by 30%, while the acute insulin response to hyperglycemia did not change. The absence of acute insulin response in the face of decreased insulin sensitivity indicated impaired β-cell response in maintaining glucose homeostasis, another contribution to impaired glucose metabolism by the use of PI[37]. Further study carried out in *in vivo* rodent islets and *in vitro* insulinoma cell line MIN6 demonstrated that the intravenously administered indinavir significantly suppressed

the first-phase insulin response in rats during the hyperglycemic clamps. The uptake of 2-deoxyglucose (which will not undergo intra-cellular metabolism) in MIN6 cells was also inhibited, suggesting a decreased sensitivity of β-cells to glucose-stimulated insulin secretion. Insulin secretagogues acting downstream of glucose transport could mostly reverse the indinavir-mediated inhibition of insulin release in MIN6 cells. It is concluded from this study that, together with peripheral insulin resistance, β-cell dysfunction likely also contributes to altered glucose homeostasis associated with ART[38].

Weight gain has long been considered a risk factor to the development of diabetes and metabolic syndrome, and has been a major concern in introduction of new anti-viral therapies to HIV infection management when cumulative evidences have led to understanding of impact of weight gain on the development of these metabolic disorders before or after anti-viral treatment[39-42]. The revolutionary development of inhibitors of the reverse transcriptase and protease and the introduction of regimens that combine these agents to enhance the overall efficacy and durability of therapy had led to profound and durable viral suppression and substantial immune system recovery. Further development and application of novel therapies that inhibit another essential HIV-1 enzymes [integrase strand transfer inhibitor (INSTI)] has not only strengthened the probability of achieving and maintaining optimal virologic suppression as first-line combination regimens in treatment-naïve patients, but also helped achieve sustained suppression of viremia in treatment-experienced patients. Clinical trials on raltegravir, the first approved INSTI for clinical use, have demonstrated safety and efficacy in both treatment-naive and pre-treated HIV-infected patients[43-47]. In a study comparing clinical effects and side effects between raltegravir-based and efavirenz-based (NNRTI) therapies in treatment-naïve HIV patients, a durable antiretroviral effect of raltegravier therapy has shown non-inferiority to the use of efavirenz. Laboratory tests on lipid profile revealed that mean changes from baseline in total cholesterol, low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were smaller in patients receiving raltegravir than efavirenz at the end of this 96-weeks' study ($p < 0.001$ for each comparison). The mean change from baseline glucose levels at week-96 was slightly less in the raltegravir group (2 mg/dL) than in the efavirenz group (6 mg/dL) ($p = 0.025$). Analysis of body fat content by dual-energy X-ray absorptiometry (DEXA) in a subset of patients showed similar degrees of fat gain in both treatment arms, with a greater increase in trunk than limb adiposity[46]. On the other hand, in treatment-experienced patients, laboratory assessment in the BENCHMRK 1 and 2 Phase III Trials reported similar changes of glucose concentrations from baseline to the 96-week study end, the range of which was pre-specifically defined as 251- 500 mg/dL (percentage of patients 2.7% vs 2.2%, statistically non-significant), whereas no patient had shown glucose levels > 500 mg/dL in either group[47]. Distinctive from other antiretroviral drugs, especially PIs which are well known to alter glucose and lipid metabolism, these side effects appeared only in rare case report in patients treated with INSTIs[48]. Since weight gain is risk factor for development of cardiovascular diseases (CVD) in both the general population and PLHIV, any of the ART that could induce significant increase in weight deserves further investigation to find its possible link with development of CVD which has long been noted to be significantly higher in HIV-infected subjects than the general population[49]. In a study carried out in treatment-naïve HIV-infected patients, 328 patients (90% male, 44% white non-Hispanic) were randomized into groups receiving tenofovir disoproxil fumarate (TDF)-emtricitabine (both NRTIs) plus atazanavir-ritonavir, darunavir-ritonavir, or raltegravir regimen over a 96-week

study period, and CT and DEXA scanning were used to assess changes in peripheral and central fat distribution, as well as lean body mass. Imaging found apparent increases in limb fat, subcutaneous and visceral abdominal fat, trunk fat (13.4%, 19.9%, 25.8%, 18%, respectively), as well as lean mass (1.8%) ($p < 0.001$ for changes within each treatment arm), but all the changes measured were not different between the PI arms or between the INSTI and the combination PI arms[50]. On the other hand, significant weight gain or changes in adiposity distribution on use of INSTI-based ART has been observed in clinical studies conducted in HIV-infected women. In the Women's Interagency HIV Study (WIHS), the participants who were assigned either switching to or added an INSTI to ART (the SWAD group, N = 234) were compared to those on regimens composed of non-INSTI ART (the STAY group, N = 884). Assessment including body weight (BW), BMI, percentage body fat (PBF), circumferences of waist, hip, arm, and thigh was performed 6-12 months before and 6-18 months after the INSTI switch/add in the SWAD participants, which was mirrored in the STAY participants. After a mean follow-up period of 2 years, the SWAD group experienced greater increases of 2.1 kg in BW, 0.8 kg/m^2 in BMI, 1.4% in PBF, and 2.0, 1.9, 0.6, and 1.0 cm in respective circumferences measured, as compared to the STAY group (all p values < 0.05). The authors concluded that, in this cohort of HIV-infected women, a switch to INSTIs was associated with significant increases in BW, fat percentage, and body circumferences, as compared to non-INSTI ART, whereas the INSTI type did not show differences in magnitudes of these changes[51]. Another randomized clinical study comparing efficacy and safety of dolutegravir versus efavirenz in treatment-naïve HIV-1-infected adults carried out in sub-Saharan Africa [the New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) trial] had shown non-inferiority in efficacy of dolutegravir-based regimen compared to the low-dose efavirenz-based reference regimen. However, other clinical assessment had noted significantly greater median increase in BW in the dolutegravir group than in the efavirenz-based group (5.0 vs. 3.0 kg, $p < 0.001$). Weight gain of at least 10% was observed more in female than the male counterpart (38.8 vs 22.9%, $p < 0.001$), and more in participants who had a low BMI at baseline[52]. The participants recruited in these randomized trials are predominantly black in race, and the majority are females. From the studies on assessment of weight changes published so far, it seems that female and black people are more likely to have weight gains on INSTI-based therapy, and especially so when compared with those which are based on NRTIs[53,54].

The diagnosis of DM in PLHIV

The diagnostic criteria for DM in PLHIV do not differ from those used in the general population except that glycated hemoglobin (HbA1c), when used for a screening or diagnostic purpose, must be interpreted with caution. In a retrospective study examining the sensitivity and specificity of HbA1c test in diagnosis of DM, the performance of a cutoff value of ≥ 6.5% used in the general population did not match that of 5.8% (a lower cut-off level), when the diagnosis was affirmed by using fasting plasma glucose (FPG) of ≥ 126 mg/dL as another standard measurement in determining the glycemic status. Calculation of fructosamine-glucose discordance revealed fructosamine, the product of glycation of serum proteins used as another index of glycation levels that prevail in shorter time duration than HbA1c represents, reliably predicted glycemia and was not influenced by mean corpuscular volume (MCV) of peripheral red blood cells[55]. In earlier

studies examining the performance of HbA1c test in HIV-infected subjects compared to non-HIV-infected DM control, HbA1c levels inversely correlated with MCV in HIV-infected DM subjects and underestimated plasma glucose levels by 29 mg/dL[56] or HbA1c by 1.32%[57], when compared to HIV-uninfected controls. In a prospective study comparing HbA1c discordance (defined as observed HbA1c – expected HbA1c ≤ - 0.5%) between 1,357 HIV-infected men and 1,500 HIV-uninfected men during a follow-up period of 13 years, it was found that at a FPG level of 125 mg/dL, the median HbA1c among HIV-infected men was 0.21% lower than among HIV-uninfected counterpart, and the magnitude of this effect increased with fasting glucose levels higher than 126 mg/dL. Among these regular semi-annual assessments, 63% of HIV-infected men had at least one visit with clinically significant HbA1c discordance. The independent risk factors associated with the discordance included (1) low CD4 cell count (< 500 cells/mm^3); (2) a regimen containing a PI, a NNRTI, or zidovudine; (3) high MCV; and (4) abnormal corpuscular hemoglobin. The authors concluded that HbA1c underestimates glycemia in HIV-infected patients. Physicians should be cautious of its use in patients with the above risk factors for HbA1c discordance, which may lead to under-diagnosis and to under-treatment of established DM[58]. Whether the use of ART contributed to the underestimated HbA1c is not a consistent finding among different studies. A prospective analysis among 10,259 HIV-infected adults initiating first-line ART in South Africa had found an improvement of anemia occurring after ART use, and the magnitude of hemoglobin increase was linearly related to CD4 count in the first 6 months of therapy. Poor nutritional status might play a role in the etiology of anemia[59]. Nutritional factors (such as deficiency of vitamin B12 or folate) might also contribute to development of macrocytic anemia in HIV-infected individuals[60]. Higher MCV values are a marker of a greater proportion of younger erythrocytes that have had a shorter time to become glycated due to greater RBC turnover in the HIV-infected group, explaining an underestimated HbA1c level relevant to ambient glycemia status. In view of constant findings of underestimation of glycemic status by the HbA1c test, either the use of HbA1c in conjunction with FPG[55] or a standard 75-g OGTT has been suggested to be the more appropriate test applied to the screening or diagnosis of DM in HIV-infected individuals[61].

Treatment of DM in PLHIV

Life style modification

Since the introduction of HAART and more effective treatments for AIDS, there has been a dramatic shift from the weight loss and wasting that had once characterized HIV/AIDS to healthier weight, or even overweight and obesity at rates mirroring those seen in the general population. In a prospective study spanning over 10 years, significant increases in both BW and BMI were noted in 92 HIV-infected subjects after treatment of HAART for 12 months (80.0 to 84.4 kg, $p < 0.0001$; 26.4 to 27.9 kg/m^2, $p < 0.0001$; respectively). During the HAART, overweight/obesity (defined as BMI ≥25 kg/m^2) prevalence increased from 52% to 66%, with a notable 27% relative increase ($p = 0.002$). Risk factors for weight gain included female sex, PI-based HAART, and in patients having a pretreatment CD4 count < 200 cells/mm^3 [62]. In the DAD (Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort) study, a longitudinal follow-up for 5 years on the incidence rate of newly developed CVD (a composite of MI, stroke, and coronary procedures) and newly diagnosed DM after first years of ART using changes in BMI as independent variable were analyzed. A total of 97 CVD events occurred in 43,982 PY (N = 9,321) and 125 diabetes events in 43,278 PY (N = 9,193). The incidence rate ratios (IRR) of CVD/unit gain in BMI in the first year of ART, when cat-

egorized by pre-ART BMI, were as follows: underweight: 0.90; normal: 1.18; overweight: 0.87; and obese: 0.95. For incident diabetes, the IRR/unit gain in BMI was 1.11, regardless of pre-ART BMI. The authors concluded that short-term gain in BMI following ART initiation increased the longer term risk of CVD in those with pre-ART BMI in the normal range, whereas the higher risk of incident diabetes occurred regardless of pre-ART BMI[42]. Factors that could have attributed to these findings may include the "return to health" weight gain with reversal of the catabolic effects of HIV infection following HAART-initiation, strategies for earlier HAART-initiation in the course of HIV infection which have prevented many PLHIV from developing wasting, in addition to exposure to the modern obesogenic environment[4,41]. As such, the initial strategy for prevention or management of DM in PLHIV would not be different from those in general population who also need intensive watch over life-style modification, mainly on proper dietary control and exercise program. Over a 12-week weight loss program conducted in obese (BMI > 30 kg/m^2), HIV-infected women, BW decreased by 6.7 ± 4.2 kg. The weight lost was 95.5% of fat with distribution both in the subcutaneous and visceral regions as evaluated by DEXA and MRI. However, lack of improvement in metabolic parameters suggests that additional interventions may be necessary to reduce the risk of DM and CVD in this population[63]. In a cohort of 50 HIV-infected patients with metabolic syndrome who have been treated with ART for a mean of 6±1 years, a randomized, placebo controlled, 2x2 group factorial study was carried out to assess changes in coronary artery calcification (CAC, which signifies a greater risk of predicted coronary heart disease when elevated) and calcified plaque volume (CPV) as assessed by CT scanning, and cardiovascular and metabolic parameters derived from blood tests. Study subjects were randomly assigned to one of four groups: 1) no lifestyle modification (no LSM) + placebo; 2) LSM + placebo; 3) no LSM + metformin; or 4) LSM + metformin. At the end of this one year intervention study, the authors found that metformin-treated subjects demonstrated significantly less progression of CAC (−1±2 vs. 33±17, p=0.004, metformin vs. placebo), whereas the effect of LSM on CAC progression was not significant (8±6 vs. 21±14, p=0.82, LSM vs. no LSM). Metformin-treated subjects also demonstrated less progression in CPV and improved HOMA-IR compared to placebo. Subjects randomized to LSM vs. no LSM showed significant improvement in HDL-C, hsCRP levels, and cardiorespiratory fitness. The authors postulated that the potential mechanism by which metformin could affect plaque progression was via activation of AMP-activated protein kinase (AMPK)[64]. The activation of AMPK by metformin not only suppresses hepatic gluconeogenesis with reduction of ambient blood glucose but also has been considered beneficial in promoting cardiovascular homeostasis by ensuring an optimum redox balance on the heart and vascular tissues, and appear to deliver their protective/therapeutic effects via modulation of AMPK signaling[65,66].

Pharmacological therapies

As for the treatment strategy for DM in PLHIV, a longitudinal follow-up for one year in evaluating the effectiveness of various initial oral anti-diabetic (OAD) agents (be it metformin, sulphonylurea, or thiazolidinedione) in HIV-infected veterans in the US had noted that the changes of HbA1c did not differ from those in uninfected control group[67]. However, certain clinical, pathophysiological, and pharmacological aspects still exist that are specific to HIV-infected individuals with DM, and may warrant special considerations in the prescription of anti-diabetic agents[68,69] (Table 1).

Metformin

Metformin is still recommended the first line

Table 1. Oral anti-diabetic Medications with Special Considerations in PLHIV

Name	Mechanisms of action	Special considerations in PLHIV
Biguanide (Metofrmin) ・the drug of first choice	・Suppress hepatic glucose production through enhancing insulin sensitivity	・Lactic acidosis may be caused by certain NRTIs (e.g. stavudine) ・Dolutegravir increases metformin concentration and dose reduction is required
Sulphonylureas	・Stimulate insulin secretion	・Risk of hypoglycemia higher than non-insulin-secretagogues ・Useful in patients aiming to gain weight
Thiazolidinedione (Pioglitazone)	・Increase insulin sensitivity (mainly in skeletal muscles)	・Contraindicated in heart failure and active hepatocellular disease ・Check liver enzymes before prescription to rule out HAART-associated hepatotoxity
Gliptins (DPP4 inhibitors)	・Raise incretin levels ・Stimulate insulin secretion ・Suppress glucagon secretion	・Saxagliptin interacts with CYP3A4 inhibitors (e.g. ritonavir, efavirenz, and cobicistat), a lower dose is considered in prescription
SGLT2 inhibitors	・Increase renal excretion of glucose	・Genital infection (mycotic), esp. in female subjects should be concerned ・Increase in dose of canagliflozin may be considered

Source: Adapted and modified from Monroe AK, Glesby MJ, Brown TT. (68); Avari P & Devendra S. (69).

OAD agent unless otherwise contraindicated. Metformin may exaggerate lipoatrophy which is not favored by patients already having such clinical features. Certain NRTIs have been noted to have higher risk of causing lactic acidosis (e.g. stavudine). Mitochondrial toxicity from these medications was considered the cause of increased lactic acid production. In addition to their high affinity for the viral enzyme reverse transcriptase, NRTIs can also bind to other human DNA polymerases, including the mitochondrial DNA polymerase-gamma, which is exclusively responsible for the replication of mitochondrial DNA (mtDNA). By inhibiting mtDNA enzyme polymerase-gamma, NRTIs can lead to depletion of mtDNA, resulting in organelle dysfunction and impairment of oxidative phosphorylation. A disturbed tight coupling oxidative phosphorylation system thus incurred will give rise to a disturbed redox state, which in turn shifts the pyruvate/lactate equilibrium in the direction of lactate, and lactic acidemia or even lactic acidosis may follow[70]. Cases of nucleoside-associated lactic acidosis have been repeatedly reported and might occur as soon as one month or as late as 20 months after the start of use. With this notion in mind, the occurrence of clinical symptoms or signs including fatigue, nausea, vomiting, or abdominal pain warrants further research into the causes[71-73]. Dolutegravir, INSTI used in treatment of HIV infection, significantly increased metformin plasma exposure, and a reduction in the dose of metformin is considered when these two medications are co-administered[74].

Sulphonyulureas (SUs)

Sulphonyulureas (SUs) stimulate pancreatic β-cell insulin secretion and would be rational for the control of blood glucose in HIV-infected DM subjects, whose insulin secretion function has been noted to be impaired. Although insulin resistance has been found to be the main cause of glucose dysregulation in HIV-infected subjects receiving HAART[33-36], the use of SU can be a useful adjunct to insulin sensitizers not only as an insulin secretagogue capable of overcoming insulin resistance but may also help gain weight in patients who are underweight[75].

Thiazolidinedione (TZD)

Thiazolidinedione (TZD), an insulin sensitizer,

can also be prescribed in HIV-infected patients with DM who have evident insulin resistance caused by HAART. Contraindications to its use do exist, including severe cardiac or hepatic disorders[76]. Potential hepatotoxicity caused by HAART should be carefully evaluated before prescribing TZD[77]. The role of gaining weight through accumulation of subcutaneous fat from its use in patients with lipoatrophy was found to be only modest, hence not considered an extra benefit in addition to its recognized role in treating diabetes and dyslipidemia (lowering of TG and rising of HDL-C) [78].

Insulin

Insulin therapy, as in the management of diabetes in general population, should always be considered in patient presenting with very high initial HbA1c as contemporary guidelines delineates, who are usually accompanied by a catabolic status from severe hyperglycemia[79]. In HIV-infected patient with lipoatrophy, the anabolic effect of insulin therapy may add further benefit with weight gain.

Incretins or sodium-glucose co-transporter-2 inhibitors

Not many clinical researches have been carried out as far on the effectiveness of newer anti-diabetic agents (incretin therapies or sodium-glucose co-transporter-2 inhibitors) in HIV-infected patients with diabetes, and drug safety is instead the issue more concerned. While gliptins (DPP4 inhibitors) have molecular targets on immune cells, a pilot study carried out in healthy, non-diabetic HIV-infected adults showed that sitagliptin did not adversely affect immune or virological status when changes in CD4 or HIV RNA were evaluated, but did improve glycemic metabolism when evaluated by area-under-the-curve of glucose concentrations in a standard 75-g OGTT as compared to the placebo group[80]. Saxagliptin interacts with strong CYP3A4/5 inhibitors (e.g. atanazavir, indinavir, or ritonavir in the PI class, efavirenz in the NNRTI class, cobicistat) and a reduction of saxagliptin dose to 2.5 mg daily is advised when co-administered with CYP3A4/5 inhibitors[81]. Glucagon-like peptide-1-receptor agonist (GLP1-RA), also an incretin therapy, has gained much attention with its additional benefits in T2DM patients with history of established CVD and in those with CVD risk factors[82]. However, there has been no well-designed clinical studies as far on the clinical effects of GLP1-RA in HIV-infected patients with DM, although rare case report has been published in the literature that the replacement of insulin therapy by exenatide in an HIV-infected T2 DM patient has resulted in not only improvement in glycemic control, but also improved insulin sensitivity and pancreatic β-cell function[83]. Similar findings were reported on the effects of liraglutide added to existing insulin therapy that had brought about improved HbA1c, along with reduced BW and dosage of insulin. The benefits of these GLP1-RAs were considered to be associated with its effect on BW and body fat distribution[84].

A switch between different classes of ART may help alleviate the risk of DM development in PLHIV who already are at higher risk, including having a history of gestational DM, family history of diabetes, or obesity. Whereas indinavir clearly causes decreased insulin sensitivity when administered to healthy, HIV-uninfected volunteers[33,34], the relative effects of other PIs have not been such clearly discerned in vivo. In vitro data concerning insulin resistance and diabetes associated with PI use, however, do suggest that certain other drugs within the class may induce insulin resistance[36,37]. There are clinical studies showing a switch from a PI to abacavir or efavirenz [85,86] appears to have a favorable effect on insulin resistance. From the above evidences, substituting an alternative drug for a PI may therefore be a reasonable strategy for patients with higher risk for development of DM. Of note is that, under any circumstances when there is a concern

for switch between the HAART regimens, a competent specialist well-experienced in management of PLHIV must be consulted for a successful and continuous care of the patients in such need.

Other than the aforementioned factors concerned in prescription of anti-diabetic agents, treatment strategies of DM in PLHIV are not much different from those in the non-HIV population. A multifactorial approach is required to include not only glycemic control, but also proper management of lipid disorder and hypertension, on top of life style modification which forms the basis of life-long managed care of this chronic disease.

Sodium-glucose co-transporter-2 inhibitor (SGLT2i)

The inhibition of urinary glucose reabsorption via the proximal renal tubules with inhibition of SGLT2 has been shown in randomized clinical trials not only could bring about reduction of plasma glucose but also benefits in protection of cardiovascular and renal diseases which are frequent comorbidities of T2DM[87]. In obese patients, the use of SGLT2i may also reduce BW when desired. So far, there has been yet well-designed clinical trials testing the efficacy of this new class of anti-diabetic agent in HIV-infected patients with DM. Nevertheless, certain pharmacological concerns must be bore in mind when prescribing this class of drugs. While no interactions between ART and dapagliflozin are expected, when UDP-glucuronosyltransferase enzyme inducers (eg, ritonavir) is co-administered with canagliflozin, clinicians might consider increasing the dose of canagliflozine since the area under the curve of canagliflozin could be significantly reduced, with a decrease in its clinical efficacy. For patients with eGFR $\geq$ 60 mL/min/1.73 m^2, the dose of canagliflozin could be up-titrated to 200 mg/day, and even 300 mg/day when clinically required for purpose of glycemic control. For those with lower eGFR < 60 mL/min/1.73 m^2, the dose of canagliflozin may be up-titrated to 200 m/day, and other anti-diabetic agents added for glycemic control[88].

Conclusion

The successful introduction and application of HAART to PLHIV in the past 2 decades and more has been shown to triumph over this once devastating infectious disease and turn it into a chronic one. With time, the longer life span in treated PLHIV mirrored the reduced morbidity and mortality after HAART. However, the figure of incidence of non-communicable diseases as PLHIV age becomes more and more prominent. DM is one that deserves high clinical attention due to the highly associated risk of cardiovascular events once DM is established. NOD in PLHIV has been noted to occur mostly after longer time use of HAART and both insulin resistance and impaired pancreatic β-cell insulin secretion have been recognized as the major underlying pathophysiological processes. It is prudent for concerned clinicians to realize the clinical significance of this entity and conduct timely diagnosis and deliver efficacious and tailored therapy to this population of PLHIV who may suffer from a new disease while an existing one has been successfully managed.

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感染人類免疫缺乏病毒患者罹患糖尿病時之治療：文獻回顧

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摘　要

隨著醫學研究對於「人類免疫缺乏病毒」的日漸瞭解，因其而罹患「後天免疫缺乏症候群」的患者得以獲得有效的抗病毒藥物治療，不僅因此可避免各類致命的伺機性感染，同時壽命亦隨之延長。這些得到適當治療的病患已隨著大眾逐漸邁入高齡化的時代，因此伴隨老化而來的非傳染性疾病漸次浮現，較顯著者如糖尿病，及伴隨其而來的心血管病變風險因子，皆需在醫療及公共衛生層面上另外加以關注。感染人類免疫缺乏病毒者在持續接受高效能抗愛滋病毒藥物治療的時期，在諸多流行病學的研究已被證實某些藥物較易導致糖尿病的發生。實驗室的研究發現：藥物所導致胰島素阻抗性的發生及胰島素分泌能力下降，是引致血糖無法保持正常代謝、甚至進展成糖尿病的主要病生理機制。在感染人類免疫缺乏病毒患者之糖尿病篩查或診斷，建議勿以糖化血色素之測量為主要參考依據，因為患者的紅血球組成異常易低估真實的血糖濃度，此時應用口服葡萄糖耐量測驗較為準確。處方治療糖尿病的各類藥物時，其選擇與使用原則與一般糖尿病患族群無太大差異，但須注意當與其他抗病毒藥物同時使用時，需有特殊考量，以避免因藥物交互作用而產生副作用，在臨床考量上值得注意。