DIABETES IN PEOPLE LIVING WITH HIV

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ABSTRACT

People living with HIV (PLWH) are living longer and also have unique risk factors for developing several metabolic diseases, including diabetes. This has been observed in both high income and low to middle income countries. Risk factors for diabetes in PLWH consist of specific antiretroviral therapies (ART), including older generation protease inhibitors and nucleoside reverse transcriptase inhibitors, lipodystrophy, and hepatitis C co-infection. In addition, obese and overweight states are common in PLWH, and an increased risk of incident diabetes has been noted with weight gain after ART initiation in PLWH, compared to individuals without HIV. Inflammation associated with HIV has also been linked to incident diabetes. This chapter reviews points to consider in the diagnosis and monitoring of diabetes in PLWH and discusses interactions that may occur between specific ART agents and glucose-lowering medications. Moreover, PLWH have risk factors for complications involving organ systems that are also affected by microvascular disease in diabetes. Because PLWH have a greater risk for cardiovascular disease (CVD) than individuals without HIV, modifiable risk factors of CVD should be addressed in the care of PLWH, considering that dyslipidemia, hypertension, and cigarette smoking are all highly prevalent in PLWH.

BACKGROUND

HIV infection is prevalent in 38.4 million people worldwide as of 2021 (1) and 1.2 million people in the United States as of 2019. The incidence of HIV infection has decreased from 2015 to 2019 in the United States but has remained stable in some demographic groups, including African-Americans and Latinos (2). Untreated, HIV infection can lead to opportunistic infections including cytomegalovirus disease and pneumocystosis (3) associated with AIDS, which is defined as a CD4+ cell count < 200 cells/mL. With advances in antiretroviral therapy (ART), however, HIV infection has been transformed from a disease strongly linked to AIDS and opportunistic infections into a chronic disease that is associated with several cardiometabolic consequences, including diabetes (4), heart disease (5), and other non-AIDS related illnesses such as osteoporosis (6). In part, this phenomenon is secondary to the fact that people living with HIV (PLWH) are living longer and are more susceptible to diseases of aging.

An important aspect to consider in the understanding of HIV associated cardiometabolic diseases is their growing global presence. The same factors that are associated with cardiometabolic disease prevalence in PLWH in high-income countries are also present in low-income countries, in addition to unique factors including industrialization, with resultant decreased physical activity and increased energy consumption (7) (8). As such, the care of PLWH needs to focus not only on ART but also on the management of chronic co-morbidities. This chapter will focus primarily on diabetes in PLWH.

EPIDEMIOLOGY AND RISK FACTORS FOR DIABETES IN PLWH

Epidemiology

PLWH have a unique set of risk factors that may increase their likelihood of developing diabetes. Illustrating the greater burden of diabetes in PLWH on ART, a study from 2005 on the Multicenter AIDS Cohort Study (MACS) of gay and bisexual men with (MWH) and without HIV (MWoH) found that the incidence of diabetes was found to be more than fourfold higher in MWH and that the prevalence of diabetes was 14% in MWH on ART and 7% in MWH not on ART, compared to 5% in MWoH. These differences were significant even after adjusting for age and body mass index (BMI). Of note, the majority of MWH on ART in the study were on first generation protease inhibitor (PI) therapy (discussed further in the section Protease Inhibitors) (9). Other studies have described incidence rates of diabetes in PLWH of 4.4 cases per 1000 person-years of follow-up in the Swiss HIV Cohort Study (10) and 5.72 cases per 1000 person-years of follow-up in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study of participants from Europe, the US, Australia, and Argentina (11).

The effect of HIV disease on developing diabetes is also growing in low- and middle-income countries (LMIC), where the majority of the people with diabetes live (12). Prevalence of estimates of diabetes in PLWH in LMIC range from 6.8% in Chile (13) to 26% in Cameroon (14). PLWH and diabetes in LMIC are younger than those in high income countries (15). The wide range of prevalence estimates of diabetes in PLWH in LMIC may be in part because of differences in the definitions used to identifying diabetes. In addition to factors common to PLWH globally, urbanization may be a contributing factor to the development of diabetes in PLWH in LMIC (16).

Antiretroviral Therapy (ART)

PROTEASE INHIBITORS (PI)

One risk factor for developing diabetes in PLWH is PI use. In 1995, saquinavir became the first FDA approved PI (17). Incidence rates of hyperglycemia as high as fivefold have been reported in the setting of PI use (18). In addition, PIs, including ritonavir, have been associated with hypertriglyceridemia (19,20) and lipodystrophy (21). Mechanisms that may account for these effects are multifold. In one study, insulin sensitivity, as measured by glucose infusion rate during hyperglycemic clamp, decreased significantly after 12 weeks of PI therapy compared to baseline. A defect in beta cell function, in particular, a decrease in the disposition index, was also observed after PI therapy (22). An *in vitro* study demonstrated that indinavir may lower the function of the glucose transporter GLUT4 (23). Additional mechanisms may include changes in the hormone adiponectin, which is associated with improved insulin sensitivity, although *in vivo* and *in vitro* effects of PIs on adiponectin have differed (24,25).

The prescribing patterns of PI use have evolved. One study found that in the Veterans Affairs system, the prevalence of PI based regimen use decreased from 1997 to 2004 (26). In addition, the effects of all PIs, namely older generation versus newer generation PIs, including atazanavir and darunavir, on glucose homeostasis are not equal. In an *in vitro* study, atazanavir, which received FDA approval in 2003 (27), did not inhibit either GLUT1 or GLUT4 glucose transporters (28). In a clinical study of HIV-participants, atazanavir in combination with ritonavir had a significantly lower effect on insulin sensitivity compared to lopinavir/ritonavir, as measured by glucose disposal rate during hyperinsulinemic euglycemic clamp. (29). Moreover, the newer generation PIs have not been associated with an increased incidence of diabetes, with one study showing a lower risk of diabetes in individuals on these medications (30).

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

In addition to PIs, certain nucleoside reverse transcriptase inhibitors (NRTIs) have been associated with diabetes. In the D:A:D study, incident diabetes was associated with exposure to the NRTIs stavudine and zidovudine, both thymidine analogs, and didanosine, after adjusting for age, sex, race, and BMI (11). NRTIs have also been implicated in mitochondrial dysfunction, which may be another mechanism by which NRTIs are associated with diabetes. One study found that one month of treatment with stavudine was associated with significant decreases in mitochondrial DNA from muscle biopsies and insulin sensitivity, as measured by the glucose infusion rate during a hyperinsulinemic euglycemic clamp (31). Because of serious adverse effects linked to the use of these NRTIs, stavudine, zidovudine, and didanosine are not advised for use in the United States (32).

Similar to the newer generation of PIs, the use of newer NRTIs, including emtricitabine, abacavir, and tenofovir, have been associated with a lower risk of diabetes (30). Supporting this finding, tenofovir disoproxil fumarate (TDF), in a study of participants without HIV or diabetes, did not significantly affect insulin sensitivity, as measured by hyperinsulinemic euglycemic clamp (33).

Tenofovir alafenamide (TAF) is a newer prodrug of tenofovir and is associated with less renal and bone toxicity than TDF (33a). However, TAF has been associated with weight gain in PLWH, compared with TDF (33b). Weight gain leading to an overweight state or obesity is a risk factor for the development of type 2 diabetes. In a retrospective study of the ADVANCE trial, which included ART naïve PLWH randomized to 3 treatment arms, 2 of which included TDF and 1 of which included TAF, an increase in the 10-year predicted risk of type 2 diabetes was observed for participants in the TAF arm, compared to participants in one of the TDF arms, although the risk calculator that was used had not been validated for the population in the study (33c). On the other hand, in a cohort study of more than 4,000 PWH on a TDF-based ART regimen for at least 6 months, of whom about 80% switched to a TAF-based ART regimen and about 20% continued on a TDF-based ART regimen, TAF was associated with a significant weight gain, compared to TDF, after 18 months, but it was not associated with incident diabetes.

INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)

Integrase strand transfer inhibitor (INSTI) based regimens are among the recommended initial ART regimens for PLWH (32) (34). Reasons for this include the effectiveness of and fewer adverse effects associated with INSTIs in studies of treatment-naïve patients (34-37). However, studies have discovered

some metabolic effects of INSTIs. These include weight gain on average of 2.9 kilograms over 18 months, as observed in a retrospective study of patients who switched to an INSTI based regimen from previously being on a non-NRTI (NNRTI)-based regimen. This was in contrast to an average 0.7 kg weight gain in those participants who switched to a PI-based regimen and 0.9 kg weight gain in those who continued on a NNRTI-based regimen (38). In addition to weight gain, case reports of new onset diabetes have been reported in conjunction with INSTI use (39,40). One clinical trial compared the INSTI raltegravir to 2 boosted PI regimens and found that the increases in homeostasis model assessment-insulin resistance (HOMA-IR) in all 3 arms were not significantly different from one another, were noted by 4 weeks, and appeared to be independent of changes in visceral adipose tissue (41). However, other studies have not demonstrated an association between diabetes and INSTI use (41a) or have found that the association between INSTI use and incident diabetes varies by individual INSTI (41b).

The exact mechanisms by which INSTIs may be related to weight gain and diabetes are not known. One proposed mechanism by which INSTIs may cause hyperglycemia is their effect on magnesium, which is a necessary cation for insulin action (40). In mice, INSTI use leads to an increase in fat mass and decreases brown and beige adipocyte differentiation, leading to lower energy expenditure and weight gain (41c).

Lipodystrophy

Lipodystrophy associated with ART is characterized by either lipoatrophy in the face, arms, and legs, or lipoaccumulation that can lead to gynecomastia, dorsocervical fat tissue, and increased intra-abdominal fat, (42,43), or mixed lipodystrophy, in which lipoatrophy and lipoaccumulation occur together. As noted above, lipodystrophy has been associated with PI use (21) and with older generation NRTI use, including stavudine (44), but less commonly with the newer generation NRTI tenofovir (45). In a cross-sectional study, HIV+ men with lipodystrophy had a greater insulin resistance than men without lipodystrophy (21). Lipodystrophy has also been associated with incident diabetes (46,47).

In one study that measured body fat changes longitudinally using dual-energy x-ray absorptiometry (DXA) in PLWH on ART (specifically zidovudine and lamivudine or didanosine and stavudine in combination with nelfinavir, efavirenz, or both), 32% of participants had discordant changes in trunk and limb fat (48).

Lipodystrophy may also be persistent in patients with exposure to thymidine analogs. Although improvements in limb fat mass were reported in patients who switched from taking the thymidine analog zidovudine to the NRTI abacavir, no significant improvement was noted in self-assessment of dorsocervical fat (49).

Hepatitis C Co-Infection

25% of PLWH in the U.S. are co-infected with hepatitis C (50). Hepatitis C infection is associated with a higher risk of developing diabetes. Treatments for hepatitis C, including direct-acting antiviral treatment and pegylated interferon/ribivirin, have been found to lower the incidence of diabetes, with a larger effect in those patients with advanced fibrosis/cirrhosis. In addition among individuals who received treatment for hepatitis C, those with a sustained virologic response were less likely to develop diabetes than those without a sustained virologic response (51).

Weight Gain, Overweight, and Obesity

Weight gain that is observed after the initiation of ART in those patients with wasting associated with untreated HIV has been characterized as a "return to health" phenomenon. However, because of an emphasis on early ART initiation, the wasting that was previously seen with advanced HIV infection is less common in countries with access to ART (52). In one 2012 study conducted in Alabama, more than 40% of patients were overweight or obese at the time of starting ART. After 2 years on ART, the percentages of underweight and normal weight participants decreased significantly, and significant increases in the percentages of overweight and obese participants were observed. Having a lower baseline CD4 count and the use of a PI as a third drug were risk factors associated with a greater increase in BMI (53).

The consequences of weight gain in PLWH may be different from those in the general population. In a study of U.S. Veterans, the risk of incident diabetes with 10 or more pounds of weight gain during the first year after ART initiation in HIV+ Veterans was significantly greater than in HIV- Veterans (54).

Among cohorts of PLWH from different countries, prevalence estimates of an overweight state or obesity range from 25% to 68% (55,56). In one study of PLWH, risk factors for being overweight or obese in PLWH included increasing age and either no evidence of hepatitis C infection or evidence of cleared hepatitis C infection (57).

Inflammation

In addition to the risk factors for diabetes in PLWH outlined above, inflammation may play a role in the development of diabetes in PLWH. Systemic inflammation results from several factors: viral replication, immune activation, which leads to T cell depletion, as well as T cell loss specifically in the gastrointestinal tract, with associated translocation of microbial factors including lipopolysaccharide (58). Co-infection with viruses, including hepatitis C virus (as discussed above), hepatitis B virus, Epstein-Barr virus, and cytomegalovirus, perpetuate systemic inflammation (59).

Although ART reduces some inflammatory biomarkers in PLWH (60), there is evidence of residual inflammation, with levels of other inflammatory biomarkers in PLWH on ART that do not decrease to levels seen in HIV- individuals (61). Persistent inflammation measured months after ART initiation has been associated with incident diabetes in PLWH (62).

DIAGNOSIS OF AND MONOTORING DIABETES IN PLWH

The American Diabetes Association (ADA) recommends the use of a fasting plasma glucose, hemoglobin A1c, or a 2-hour plasma glucose after a 75-gram oral glucose tolerance test to establish the diagnosis of diabetes in the general population. However, there is a caveat that for certain populations of patients, including PLWH, fasting plasma glucose is preferable to hemoglobin A1c (63). Hemoglobin A1c has been found to underestimate glycemia in PLWH (64,65). One reason for this is the use of medications that cause hemolysis, including dapsone and trimethoprim-sulfamethoxazole, which are used for prophylaxis of *Pneumocystis jiroveci*, an opportunistic infection (65). However, another reason for the discrepancy between glucose levels and hemoglobin A1c is NRTI use. NRTIs, especially the thymidine analogs, are associated with an increased risk of macrocytosis (66), which can lower hemoglobin A1c. Finally, lower CD4 cell count (< 500 cells/mm^3) was associated with a significant discordance between expected and measured hemoglobin A1c in MWoH in the MACS (67). As such, self-monitoring of blood

glucose in PLWH may be preferable to using hemoglobin A1c for monitoring glycemic control (64).

The most recent Infectious Diseases Society of America guidelines on the primary care of PLWH recommends obtaining either a fasting plasma glucose and/or hemoglobin A1c at baseline and at 1 to 3 months after starting ART. In addition, hemoglobin A1c is preferred to fasting glucose for diagnosing diabetes because of the relative ease of obtaining a hemoglobin A1c over a fasting glucose. However, a hemoglobin A1c level ≥ 5.8% can be considered to diagnose diabetes in PLWH, instead of the ADA recommendation of ≥ 6.5%, as this improves the sensitivity of the test (68,69). Moreover, a hemoglobin A1c is recommended to be obtained every 6 months in PLWH and diabetes, with a goal hemoglobin A1c of < 7% (68).

TREATMENT OF DIABETES IN PLWH

Special considerations should be taken into account in the treatment of diabetes in PLWH. PLWH may not respond to treatment for diabetes in the same manner as HIV- individuals. Part of this observation may be because treatment responses were measured using hemoglobin A1c, which may be an inaccurate indicator of glycemia in PLWH (70), as noted above.

Interactions between several diabetes medications and ART are known. In addition, some diabetes medications may present advantages or disadvantages in PLWH. These conditions are described in further detail below and are organized by diabetes medication.

Lifestyle Interventions

Both the 2023 ADA Standards of Care on Pharmacologic Approaches to Glycemic Treatment and the 2023 updated American Association of Clinical Endocrinology algorithm of the management of type 2 diabetes highlight lifestyle interventions as part of the recommended treatment of type 2 diabetes (70a, 70b). Lifestyle interventions include not only a healthy diet and exercise but also smoking cessation and moderating alcohol intake (70b).

Physical activity has benefits for PLWH, including decreasing waist circumference (70c) and improvements in glucose and high-density lipoprotein cholesterol levels (70d). However, low physical activity has been reported in some studies of PLWH (70e, 70f).

Metformin

The 2023 ADA Standards of Care on Pharmacologic Approaches to Glycemic Treatment includes metformin as one first-line treatment to consider in patients in the general population with type 2 diabetes (70a) (71).

In PLWH with lipodystrophy and insulin resistance but without diabetes, 3 months of metformin 1000 mg twice daily was found to significantly decrease insulin area under the curve after an oral glucose tolerance test. Although no increased incidence in lactic acidosis was noted in the participants who received metformin, the study was not powered for this outcome, and liver and kidney dysfunction were exclusion criteria (72).

The commonly used integrase transfer strand inhibitor, dolutegravir, increases plasma levels of metformin, and thus adjusting the dose of metformin upon dolutegravir initiation has been recommended (73,74). However, one retrospective study found that there was no significant difference in glycemic control before and after starting dolutegravir in PLWH and diabetes on metformin (75).

In summary, there are no guidelines to suggest that metformin should not be a possible first-line treatment of type 2 diabetes in PLWH, after consideration of liver and kidney function and dolutegravir treatment.

Sulfonylureas

Sulfonylureas are a substrate of the CYP2C9 enzyme. The PIs ritonavir and nelfinavir are CYP2C9 inducers and can decrease sulfonylurea levels (76,77). In comparison with initial use of metformin in PLWH, no significant difference in glycemia after one year of therapy was noted with initial use of a sulfonylurea (78).

The 2023 ADA guidelines note that sulfonylureas are a high efficacy drug class for glucose management and are less cost-prohibitive compared to many other drug classes (70a) (71). However, adverse effects of sulfonylureas include hypoglycemia and weight gain. In PLWH, consideration should be made if a patient is on ritonavir or nelfinavir and the possible loss of efficacy of sulfonylurea treatment.

Thiazolidinediones

The effect of thiazolidinediones on glycemic control in PLWH with diabetes specifically has not been studied, although some trials found that rosiglitazone lowered serum insulin levels in PLWH without diabetes (79) and improved insulin sensitivity in PLWH with hyperinsulinemia (80). Several studies have focused on the effect of thiazolidinediones (TZDs) on body fat in PLWH with lipodystrophy, with equivocal findings. One 24-week study on the effect of rosiglitazone on PLWH, all of whom were on a PI, found no significant difference in arm fat between the treatment and placebo groups (81). However, the study did not have enough power to detect a difference in this outcome (82). On the other hand, other studies demonstrated that rosiglitazone increased visceral and subcutaneous abdominal fat in MWH with lipodystrophy over 6 months (83) and subcutaneous leg fat in PLWH with lipodystrophy over 3 months (80).

Adverse side effects of TZDs should be considered and discussed prior to initiation. These include fluid retention, osteoporosis, edema, and potential liver injury (84).

Dipeptidyl Peptidase 4 Inhibitors

Some clinical studies have demonstrated that dipeptidyl peptidase 4 (DPP4) inhibitors exert an anti-inflammatory effect in patients with type 2 diabetes (85,86). This idea was further examined in PLWH in a pilot study of 20 PLWH on ART randomized to either the DPP4 inhibitor sitagliptin or placebo for 24 weeks. A significant decrease was noted in the chemokine SDF-1α in the treatment group. In addition, an improvement in glucose tolerance was noted at week 8 in the treatment group, but the difference in glucose tolerance between the two groups was no longer significant at the end of the study (87). In another study of PLWH with impaired glucose tolerance, sitagliptin resulted in a significant improvement in glucose tolerance and decreases in the inflammatory markers hsCRP and CXCL10 from baseline after 8 weeks of treatment, compared to placebo (88). Similarly, in a larger study of 84 PLWH on ART with viral suppression and without diabetes who were randomized to 16 weeks of sitagliptin versus placebo, a significant decrease from baseline was seen at week 15 in CXCL10 in participants in the treatment group (89).

Glucagon-Like Peptide-1 Receptor Agonists

Several glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to improve weight and

cardiovascular outcomes, albeit in patient populations not specific to PLWH (90,91). Liraglutide, dulaglutide, and semaglutide have been shown to lower the risk of a composite outcome of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death in patients with type 2 diabetes (90,91). Liraglutide, semaglutide, and dulaglutide have indications from the Food and Drug Administration for lowering cardiovascular event risk in patients with cardiovascular disease and type 2 diabetes, and dulaglutide is also approved for lowering cardiovascular event risk in patients with multiple cardiovascular risk factors and type 2 diabetes. The 2023 ADA guidelines recommend the use of a GLP-1 receptor agonist as a first-line treatment in patients with cardiovascular disease and type 2 diabetes (70a).

One case report described a single PLWH who was able to discontinue insulin treatment (insulin glargine 60 units daily) and who experienced improvements in weight and hemoglobin A1c after starting liraglutide therapy (92). Another case report described improvements in hemoglobin A1c and fasting glucose on dulaglutide in a PLWH. Relatively scant literature exists on the effects of GLP-1 receptors agonists in PLWH and diabetes (93,94).

Sodium-Glucose Co-Transporter-2 Inhibitors

Similar to the GLP-1 receptor agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors have demonstrated reductions in adverse cardiovascular outcomes, including cardiovascular death and hospitalization for heart failure in general population studies (95,96). In addition, both dapagliflozin and canagliflozin have an FDA indication to reduce the risk of end-stage renal disease in patients with type 2 diabetes and diabetic nephropathy with albuminuria (96a). As such, the 2023 ADA guidelines on pharmacologic treatment of diabetes recommend that in those patients with type 2 diabetes and chronic

kidney disease, a SGLT2 inhibitor that has been shown to reduce risk of renal disease progression should be used (70a).

SGLT2 inhibitors are also approved for reduction of adverse cardiovascular events and heart failure hospitalization in people with diabetes and have cardiovascular benefits for patients with either systolic or diastolic heart failure (96a). Diastolic dysfunction is more common in PLWH compared with people without HIV. As such, the 2023 ADA guidelines recommend the use of an SGLT2 inhibitor with demonstrated benefit in patients with type 2 diabetes and heart failure (70a).

One small trial studied canagliflozin for 24 weeks in 8 obese PLWH with type 2 diabetes and hemoglobin A1c > 7% and observed improvements in weight and hemoglobin A1c at the end of the study compared to baseline (97).

Adverse side effects of SGLT2 inhibitors include genital mycotic and urinary tract infections. In addition, 55 post-marketing cases of Fournier's gangrene have been reported between March 2013 to January 2019 (98). A risk factor for Fournier's gangrene is HIV infection (99-101), especially a CD4 cell count < 200 cells/μL (102).

Insulin

The 2023 ADA guidelines recommend considering insulin initiation in the patient 1) with a hemoglobin A1c > 11%, 2) with signs and symptoms of catabolism, 3) who has a presentation concerning for type 1 diabetes, and/or 4) whose hemoglobin A1c is not at goal despite taking 2 to 3 medications for diabetes, in addition to a GLP-1 receptor agonist.

As with all patients with diabetes, side effects of insulin therapy to consider in a discussion with a patient with HIV disease and diabetes include the risks of hypoglycemia and weight gain.

Sequence of Initiating Diabetes Medications in PLWH

There are no specific guidelines for the treatment of diabetes in PLWH. The 2023 ADA guidelines recommend the treatment of type 2 diabetes be tailored to the individual patient and consider factors including cost of medications, weight loss goals, and comorbidities including chronic kidney disease, atherosclerotic cardiovascular disease, and heart failure. Healthy lifestyle interventions should be incorporated alongside the pharmacologic treatment of type 2 diabetes.

For those patients with type 2 diabetes and ASCVD or who are at high risk for ASCVD, treatment with either a GLP-1 receptor agonist or SGLT2 inhibitor is recommended. If A1c is not at goal, then adding an additional agent, 1) such as a SGLT2 inhibitor, if the patient is already on a GLP-1 receptor agonist, or a GLP-1 receptor agonist, if the patient is already on a SGLT2 inhibitor, or 2) a thiazolidinedione, is recommended (70a). For patients with type 2 diabetes and heart failure, a SGLT2 inhibitor is recommended, as noted above. For patients with type 2 diabetes and chronic kidney disease, a SGLT2 inhibitor, or if contraindicated, a GLP-1 receptor agonist is recommended. Finally, for those patients with type 2 diabetes for whom weight management is a priority, a medication with weight loss or weight neutral effects can be considered. With regards to weight loss, semaglutide and tirzepatide have the most effect, whereas metformin and DPP4 inhibitors are weight neutral. Dulaglutide and liraglutide have a high weight loss efficacy, and SGLT2 inhibitors have intermediate weight loss efficacy (70a).

In PLWH, an additional factor to consider is the possible interaction of a diabetes medication with specific ART.

MICROVASCULAR COMPLICATIONS ASSOCIATED WITH DIABETES IN PLWH

Peripheral Neuropathy

HIV is associated with multiple peripheral neuropathies (PNs), including a distal, symmetric polyneuropathy (DSPN) (103). The prevalence of HIV-associated PN among PLWH varies < 10% to upwards of 50%, with the wide variability in prevalence estimates secondary in part to differences in methods used to assess PN (104). Risk factors for HIV-associated DSPN include use of the NRTIs zalcitabine, didanosine, and stavudine (105). In addition, HIV-associated DSPN has been observed in PLWH within 1 year of HIV transmission and is significantly associated with evidence of immune activation present in the central nervous system (106).

HIV-associated PN, in addition to the risk of developing PN secondary to diabetes, may place PLWH and diabetes at increased risk of sequelae including falls, particularly in those PLWH with a detectable viral load (107), foot ulceration, and amputations.

In summary, in addition to considering the risk of diabetic peripheral neuropathy, the risk of HIV-associated PNs should be kept in mind in the assessment and treatment of PLWH with diabetes.

Nephropathy

The prevalence estimates of chronic kidney disease (CKD) in PLWH vary depending on geographic region,

with 7.9% of PLWH affected in Africa (with the highest prevalence among African regions in West Africa at 22%), compared to 3.7% in Europe. In addition, prevalence estimates of CKD in PLWH are significantly greater among those individuals with co-morbid diabetes (108). In the MACS, two independent risk factors associated with greater odds of proteinuria were HIV+ serostatus with ART use, compared to HIV-serostatus, and a history of diabetes (109). Moreover, glomerular hyperfiltration, or a supranormal estimated glomerular filtration rate, is more prevalent among HIV+ men without CKD than HIV- men without CKD (110). Glomerular hyperfiltration has been reported to be an initial state of dysfunction seen in patients with diabetic kidney disease and proteinuria (111).

Other risk factors for CKD in PLWH include the following: recurrent acute kidney injury, African-American race, in part because of risk variants of the APOL1 gene, and persistent inflammation, even in the setting of ART (112-114). In addition, an HIV-associated nephropathy (HIVAN), which is characterized by several insults to the kidney, including focal and segmental glomerulosclerosis, exists. Certain ART drugs within the NRTI, NNRTI, and PI classes are also associated with renal injury (114). Among these are the NRTI tenofovir, which is associated with adverse kidney disease outcomes independent of diabetes (115), and the PI indinavir (116).

Retinopathy

Ocular opportunistic infections in PLWH include CMV retinitis and ischemic HIV retinopathy (117). In addition, patients with a history of CMV retinitis should be monitored periodically for retinitis recurrence by an ophthalmologist (118). However, these ocular opportunistic infections are less common in the setting of ART. However, retinal disease has been noted in PLWH on ART as part of a larger syndrome of the HIV-associated neuroretinal disorder (117), which has an incidence of more than 50% at 20 years after a diagnosis of AIDS (119). One study found that among HIV+ men with a median duration of ART use of 12 years and suppressed viremia did have a significant difference in total peripheral retinal thickness from HIV- men, although the long-term clinical relevance of this is unknown (117).

There is limited literature on the effect of co-morbid diabetes on HIV-associated retinal disease.

MODIFIABLE FACTORS OF MACROVASCULAR COMPLICATIONS ASSOCIATED WITH DIABETES IN PLWH

PLWH are at increased risk of developing atherosclerotic cardiovascular disease (ASCVD) compared to individuals without HIV, despite controlling for traditional cardiovascular (CV) risk factors such as diabetes (5,120). In addition, PLWH have a greater burden of traditional CV risk factors (120). Other non-traditional risk factors include some ART such as older generation PIs (121) and inflammation (122). As such, calculators developed for the general population to calculate ASCVD risk may not accurately capture risk in PLWH (123).

Aspirin

Recent American College of Cardiology/American Heart Association (ACC/AHA) recommend the use of aspirin for primary prevention of ASCVD in general population patients age 40 to 70 years with high ASCVD risk (124), and similarly the American Diabetes Association (ADA) guidelines also recommend aspirin use in select patients with diabetes < 70 years of age with high ASCVD risk and low bleeding risk (125). However, evidence has shown that aspirin use is lower in PLWH with CV risk factors

than in HIV- individuals (126), and PLWH are less likely to be prescribed aspirin for primary prevention than HIV- individuals (127).

Blood Pressure

The prevalence of hypertension globally in PLWH is substantial. PLWH have several risk factors for developing hypertension, including a greater prevalence of smoking (as noted below) (128,129) and ART use (130). The relationship of ART to hypertension is thought to be in part from its association to weight gain. Moreover, in the MACS, ART use was associated with greater systolic hypertension but not diastolic hypertension. A mechanism for this could be a change in arterial compliance as a consequence of ART use (131).

The 2023 ADA guidelines recommend a goal blood pressure of < 130/80 (132).

Cholesterol

Dyslipidemia is seen in both untreated PLWH and PLWH on ART (133,134). The decision to initiate a statin in a patient living with HIV for primary prevention should take into account the patient's HIV serostatus, especially in those patients with a 10-year ASCVD risk of 5 to < 20% (124).

The primary prevention of atherosclerotic cardiovascular disease is a clinically important topic. The Evaluating the Use of Pitavastatin to Reduce Cardiovascular Disease in HIV-Infected Adults (REPRIEVE) study is a multicenter, international, randomized clinical trial on PWH on ART, in which participants with a low to moderate risk of ASCVD were randomized to either pitavastatin daily or placebo (134a). In March 2023, the Data Safety and Monitoring

Board recommended premature closure of the study based on the observed efficacy of the study treatment to reduce the primary endpoint of major adverse cardiovascular events (MACE) by 35% relative to the placebo. The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval, 0.48 to 0.90; P = 0.002). Of note, similar to other studies the risk of diabetes was increased in the pitavastatin group (diabetes mellitus occurred in 5.3% in pitavastatin group and 4.0% in the control group. These results suggest that many PLWH should be on statin therapy.

Cigarette Smoking

Cigarette smoking is more prevalent in PLWH than in individuals without HIV (129), and life expectancy is estimated to be lower in HIV+ men and women who are current smokers at the time of HIV care initiation than in HIV+ men and women who are former or never smokers, with a 2.9 year gain in life expectancy at 10 years after HIV care initiation (135). The ADA guidelines recommend that people with diabetes not smoke cigarettes and that smoking cessation treatment be offered for those patients with diabetes who do smoke (136).

SUMMARY

In summary, PLWH have unique risk factors that increase their risk of diabetes. Factors to take into consideration in the treatment of PLWH include the following: type of ART, evidence of lipodystrophy, co-infection with other viruses, and overweight or obese state. A caveat is that HbA1c may be inaccurate in diagnosing and monitoring diabetes in PLWH. PLWH have additional risk factors for developing microvascular complications of diabetes. Some

glycemic agents may interact with ART, and other glycemic agents may have unwanted effects, including weight gain, that should be addressed in a patient-provider discussion. Finally, additional modifiable cardiovascular risk factors, including hypertension and smoking, should be addressed in the comprehensive treatment of diabetes in PLWH.

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