**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/mm3) 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**

Cigarettesmoking 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.

**REFERENCES**

1. World Health Organization. <https://www.who.int/hiv/data/en/>. Accessed July 3, 2019.

2. Centers for Disease Control and Prevention. <https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/HIV-Incidence-Fact-Sheet_508.pdf>. Accessed July 3, 2019.

3. Chu C, Selwyn PA. An epidemic in evolution: the need for new models of HIV care in the chronic disease era. J Urban Health*.* 2011;88(3):556-566.

4. Duncan AD, Goff LM, Peters BS. Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. PLoS One*.* 2018;13(3):e0194199.

5. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med*.* 2013;173(8):614-622.

6. Mallon PW. Aging with HIV: osteoporosis and fractures. Curr Opin HIV AIDS*.* 2014;9(4):428-435.

7. Mohan V DM. The metabolic syndrome in developing countries. Diabetes Voice*.* 2006;51:15-17.

8. Naidu S, Ponnampalvanar S, Kamaruzzaman SB, Kamarulzaman A. Prevalence of Metabolic Syndrome Among People Living with HIV in Developing Countries: A Systematic Review. AIDS Patient Care STDS*.* 2017;31(1):1-13.

9. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. Arch Intern Med*.* 2005;165(10):1179-1184.

10. Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, Hirschel B, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. Clin Infect Dis*.* 2007;45(1):111-119.

11. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Diabetes Care*.* 2008;31(6):1224-1229.

12. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract*.* 2018;138:271-281.

13. Cahn P, Leite O, Rosales A, Cabello R, Alvarez CA, Seas C, et al. Metabolic profile and cardiovascular risk factors among Latin American HIV-infected patients receiving HAART. Braz J Infect Dis*.* 2010;14(2):158-166.

14. Ngatchou W, Lemogoum D, Ndobo P, Yagnigni E, Tiogou E, Nga E, et al. Increased burden and severity of metabolic syndrome and arterial stiffness in treatment-naive HIV+ patients from Cameroon. Vasc Health Risk Manag*.* 2013;9:509-516.

15. Ali MK, Magee MJ, Dave JA, Ofotokun I, Tungsiripat M, Jones TK, et al. HIV and metabolic, body, and bone disorders: what we know from low- and middle-income countries. J Acquir Immune Defic Syndr*.* 2014;67 Suppl 1:S27-39.

16. Patel P, Rose CE, Collins PY, Nuche-Berenguer B, Sahasrabuddhe VV, Peprah E, et al. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: a systematic review and meta-analysis. AIDS*.* 2018;32 Suppl 1:S5-S20.

17. HIV/AIDS Historical Time Line 1995-1999. <https://www.fda.gov/patients/hiv-timeline-and-history-approvals/hivaids-historical-time-line-1995-1999>. Accessed July 5, 2019.

18. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. Arch Intern Med*.* 2000;160(13):2050-2056.

19. Markowitz M, Saag M, Powderly WG, Hurley AM, Hsu A, Valdes JM, et al. A preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection. N Engl J Med*.* 1995;333(23):1534-1539.

20. Cameron DW, Heath-Chiozzi M, Danner S, Cohen C, Kravcik S, Maurath C, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet*.* 1998;351(9102):543-549.

21. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS*.* 1998;12(7):F51-58.

22. Woerle HJ, Mariuz PR, Meyer C, Reichman RC, Popa EM, Dostou JM, et al. Mechanisms for the deterioration in glucose tolerance associated with HIV protease inhibitor regimens. Diabetes*.* 2003;52(4):918-925.

23. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. J Biol Chem*.* 2004;279(53):55147-55152.

24. Lee GA, Mafong DD, Noor MA, Lo JC, Mulligan K, Schwarz JM, et al. HIV protease inhibitors increase adiponectin levels in HIV-negative men. J Acquir Immune Defic Syndr*.* 2004;36(1):645-647.

25. Xu A, Yin S, Wong L, Chan KW, Lam KS. Adiponectin ameliorates dyslipidemia induced by the human immunodeficiency virus protease inhibitor ritonavir in mice. Endocrinology*.* 2004;145(2):487-494.

26. Holodniy M, Hornberger J, Rapoport D, Robertus K, MaCurdy TE, Lopez J, et al. Relationship between antiretroviral prescribing patterns and treatment guidelines in treatment-naive HIV-1-infected US veterans (1992-2004). J Acquir Immune Defic Syndr*.* 2007;44(1):20-29.

27. Research CfDEa. <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-567_Reyataz_Approv.pdf>. Accessed July 5, 2019.

28. Hresko RC, Hruz PW. HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. PLoS One*.* 2011;6(9):e25237.

29. Noor MA, Flint OP, Maa JF, Parker RA. Effects of atazanavir/ritonavir and lopinavir/ritonavir on glucose uptake and insulin sensitivity: demonstrable differences in vitro and clinically. AIDS*.* 2006;20(14):1813-1821.

30. Spagnuolo V, Galli L, Poli A, Salpietro S, Gianotti N, Piatti P, et al. Associations of statins and antiretroviral drugs with the onset of type 2 diabetes among HIV-1-infected patients. BMC Infect Dis*.* 2017;17(1):43.

31. Fleischman A, Johnsen S, Systrom DM, Hrovat M, Farrar CT, Frontera W, et al. Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. Am J Physiol Endocrinol Metab*.* 2007;292(6):E1666-1673.

32. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/11/what-to-start>. Accessed July 5, 2019.

33. Randell PA, Jackson AG, Zhong L, Yale K, Moyle GJ. The effect of tenofovir disoproxil fumarate on whole-body insulin sensitivity, lipids and adipokines in healthy volunteers. Antivir Ther*.* 2010;15(2):227-233.

33A. Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis. Medicine (Baltimore). 2016 Oct;95(41):e5146.

33B. Sax, P. E. , Erlandson, K. M. , Lake, J. E. , Mccomsey, G. A. , Orkin, C. , Esser, S. , Brown, T. T. , Rockstroh, J. K. , Wei, X. , Carter, C. C. , Zhong, L. , Brainard, D. M. , Melbourne, K. , Das, M. , Stellbrink, H. , Post, F. A. , Waters, L. & Koethe, J. R. 2020. Weight Gain Following Initiation of Antiretroviral Therapy. Clinical Infectious Diseases, 71 (6), 1379-1389.

33C. McCann K, Shah S, Hindley L, Hill A, Qavi A, Simmons B, Serenata C, Sokhela S, Venter WDF. Implications of weight gain with newer anti-retrovirals: 10-year predictions of cardiovascular disease and diabetes. AIDS. 2021 Aug 1;35(10):1657-1665.

34. Hulgan T. Factors Associated With Insulin Resistance in Adults With HIV Receiving Contemporary Antiretroviral Therapy: a Brief Update. Curr HIV/AIDS Rep*.* 2018;15(3):223-232.

35. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet*.* 2009;374(9692):796-806.

36. DeJesus E, Rockstroh JK, Henry K, Molina JM, Gathe J, Ramanathan S, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet*.* 2012;379(9835):2429-2438.

37. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet*.* 2013;381(9868):735-743.

38. Norwood J, Turner M, Bofill C, Rebeiro P, Shepherd B, Bebawy S, et al. Brief Report: Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor-Based Regimens. J Acquir Immune Defic Syndr*.* 2017;76(5):527-531.

39. McLaughlin M, Walsh S, Galvin S. Dolutegravir-induced hyperglycaemia in a patient living with HIV. J Antimicrob Chemother*.* 2018;73(1):258-260.

40. Fong PS, Flynn DM, Evans CD, Korthuis PT. Integrase strand transfer inhibitor-associated diabetes mellitus: A case report. Int J STD AIDS*.* 2017;28(6):626-628.

41. Dirajlal-Fargo S, Moser C, Brown TT, Kelesidis T, Dube MP, Stein JH, et al. Changes in Insulin Resistance After Initiation of Raltegravir or Protease Inhibitors With Tenofovir-Emtricitabine: AIDS Clinical Trials Group A5260s. Open Forum Infect Dis*.* 2016;3(3):ofw174.

41A. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, Perrineau S, Lantche Wandji M, Tetsa Tata D, Omgba Bassega P, Abong Bwenda T, Varloteaux M, Tongo M, Mpoudi-Ngolé E, Montoyo A, Mercier N, LeMoing V, Peeters M, Reynes J, Delaporte E; Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group. Lancet HIV. 2020 Oct;7(10):e677-e687.

41B. Rebeiro PF, Jenkins CA, Bian A, Lake JE, Bourgi K, Moore RD, Horberg MA, Matthews WC, Silverberg MJ, Thorne J, Mayor AM, Lima VD, Palella FJ, Saag MS, Althoff KN, Gill MJ, Wong C, Klein MB, Crane HM, Marconi VC, Shepherd BE, Sterling TR, Koethe JR. Risk of Incident Diabetes Mellitus, Weight Gain, and Their Relationships With Integrase Inhibitor-Based Initial Antiretroviral Therapy Among Persons With Human Immunodeficiency Virus in the United States and Canada. Clin Infect Dis. 2021 Oct 5;73(7):e2234-e2242.

41C. Jung I, Tu-Sekine B, Jin S, Anokye-Danso F, Ahima RS, Brown TT, Kim SF. Dolutegravir Suppresses Thermogenesis via Disrupting Uncoupling Protein 1 Expression and Mitochondrial Function in Brown/Beige Adipocytes in Preclinical Models. J Infect Dis. 2022 Nov 1;226(9):1626-1636.

42. Baril JG, Junod P, Leblanc R, Dion H, Therrien R, Laplante F, et al. HIV-associated lipodystrophy syndrome: A review of clinical aspects. Can J Infect Dis Med Microbiol*.* 2005;16(4):233-243.

43. Carr A. HIV protease inhibitor-related lipodystrophy syndrome. Clin Infect Dis*.* 2000;30 Suppl 2:S135-142.

44. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS*.* 2000;14(10):1309-1316.

45. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA*.* 2004;292(2):191-201.

46. Nansseu JR, Bigna JJ, Kaze AD, Noubiap JJ. Incidence and Risk Factors for Prediabetes and Diabetes Mellitus Among HIV-infected Adults on Antiretroviral Therapy: A Systematic Review and Meta-analysis. Epidemiology*.* 2018;29(3):431-441.

47. Putcharoen O, Wattanachanya L, Sophonphan J, Siwamogsatham S, Sapsirisavat V, Gatechompol S, et al. New-onset diabetes in HIV-treated adults: predictors, long-term renal and cardiovascular outcomes. AIDS*.* 2017;31(11):1535-1543.

48. Mulligan K, Parker RA, Komarow L, Grinspoon SK, Tebas P, Robbins GK, et al. Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. J Acquir Immune Defic Syndr*.* 2006;41(5):590-597.

49. Martin A, Smith DE, Carr A, Ringland C, Amin J, Emery S, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS*.* 2004;18(7):1029-1036.

50. Prevention CfDCa. Coinfection with HIV and Viral Hepatitis. <https://www.cdc.gov/hepatitis/hiv-hepatitis-coinfection.htm>. Accessed July 12, 2019.

51. Butt AA, Aslam S, Yan P, Shaikh OS, Abou-Samra A-B. Incident Diabetes and Glucose Control after HCV Treatment with DAAs in Erchives. Paper presented at: Conference on Retroviruses and Opportunistic Infections 2019; Seattle, Washington.

52. Kumar S, Samaras K. The Impact of Weight Gain During HIV Treatment on Risk of Pre-diabetes, Diabetes Mellitus, Cardiovascular Disease, and Mortality. Front Endocrinol (Lausanne)*.* 2018;9:705.

53. Tate T, Willig AL, Willig JH, Raper JL, Moneyham L, Kempf MC, et al. HIV infection and obesity: where did all the wasting go? Antivir Ther*.* 2012;17(7):1281-1289.

54. Herrin M, Tate JP, Akgun KM, Butt AA, Crothers K, Freiberg MS, et al. Weight Gain and Incident Diabetes Among HIV-Infected Veterans Initiating Antiretroviral Therapy Compared With Uninfected Individuals. J Acquir Immune Defic Syndr*.* 2016;73(2):228-236.

55. Levy ME, Greenberg AE, Hart R, Powers Happ L, Hadigan C, Castel A, et al. High burden of metabolic comorbidities in a citywide cohort of HIV outpatients: evolving health care needs of people aging with HIV in Washington, DC. HIV Med*.* 2017;18(10):724-735.

56. Semu H, Zack RM, Liu E, Hertzmark E, Spiegelman D, Sztam K, et al. Prevalence and Risk Factors for Overweight and Obesity among HIV-Infected Adults in Dar es Salaam, Tanzania. J Int Assoc Provid AIDS Care*.* 2016;15(6):512-521.

57. Obry-Roguet V, Bregigeon S, Cano CE, Lions C, Zaegel-Faucher O, Laroche H, et al. Risk factors associated with overweight and obesity in HIV-infected people: Aging, behavioral factors but not cART in a cross-sectional study. Medicine (Baltimore)*.* 2018;97(23):e10956.

58. Douek DC, Roederer M, Koup RA. Emerging concepts in the immunopathogenesis of AIDS. Annu Rev Med*.* 2009;60:471-484.

59. Zicari S, Sessa L, Cotugno N, Ruggiero A, Morrocchi E, Concato C, et al. Immune Activation, Inflammation, and Non-AIDS Co-Morbidities in HIV-Infected Patients under Long-Term ART. Viruses*.* 2019;11(3).

60. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS*.* 2015;29(4):463-471.

61. Neuhaus J, Jacobs DR, Jr., Baker JV, Calmy A, Duprez D, La Rosa A, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis*.* 2010;201(12):1788-1795.

62. Brown TT, Tassiopoulos K, Bosch RJ, Shikuma C, McComsey GA. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. Diabetes Care*.* 2010;33(10):2244-2249.

63. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care*.* 2019;42(Suppl 1):S13-S28.

64. Diop ME, Bastard JP, Meunier N, Thevenet S, Maachi M, Capeau J, et al. Inappropriately low glycated hemoglobin values and hemolysis in HIV-infected patients. AIDS Res Hum Retroviruses*.* 2006;22(12):1242-1247.

65. Polgreen PM, Putz D, Stapleton JT. Inaccurate glycosylated hemoglobin A1C measurements in human immunodeficiency virus-positive patients with diabetes mellitus. Clin Infect Dis*.* 2003;37(4):e53-56.

66. Geene D, Sudre P, Anwar D, Goehring C, Saaidia A, Hirschel B. Causes of macrocytosis in HIV-infected patients not treated with zidovudine. Swiss HIV Cohort Study. J Infect*.* 2000;40(2):160-163.

67. Slama L, Palella FJ, Jr., Abraham AG, Li X, Vigouroux C, Pialoux G, et al. Inaccuracy of haemoglobin A1c among HIV-infected men: effects of CD4 cell count, antiretroviral therapies and haematological parameters. J Antimicrob Chemother*.* 2014;69(12):3360-3367.

68. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis*.* 2014;58(1):1-10.

69. Eckhardt BJ, Holzman RS, Kwan CK, Baghdadi J, Aberg JA. Glycated Hemoglobin A(1c) as screening for diabetes mellitus in HIV-infected individuals. AIDS Patient Care STDS*.* 2012;26(4):197-201.

70. Han JH, Crane HM, Bellamy SL, Frank I, Cardillo S, Bisson GP, et al. HIV infection and glycemic response to newly initiated diabetic medical therapy. AIDS*.* 2012;26(16):2087-2095.

70A. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S140-S157.

70B. Samson SL, Vellanki P, Blonde L, Christofides EA, Galindo RJ, Hirsch IB, Isaacs SD, Izuora KE, Low Wang CC, Twining CL, Umpierrez GE, Valencia WM. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. Endocr Pract. 2023 May;29(5):305-340.

70C. Jaggers JR, Prasad VK, Dudgeon WD, Blair SN, Sui X, Burgess S, Hand GA. Associations between physical activity and sedentary time on components of metabolic syndrome among adults with HIV. AIDS Care. 2014;26(11):1387-92.

70D. Roos R, Myezwa H, van Aswegen H, Musenge E. Effects of an education and home-based pedometer walking program on ischemic heart disease risk factors in people infected with HIV: a randomized trial. J Acquir Immune Defic Syndr. 2014 Nov 1;67(3):268-76.

70E. Rehm KE, Konkle-Parker D. Physical activity levels and perceived benefits and barriers to physical activity in HIV-infected women living in the deep south of the United States. AIDS Care. 2016 Sep;28(9):1205-10.

70F. Vancampfort D, Mugisha J, Richards J, De Hert M, Lazzarotto AR, Schuch FB, Probst M, Stubbs B. Dropout from physical activity interventions in people living with HIV: a systematic review and meta-analysis. AIDS Care. 2017 May;29(5):636-643.

71. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care*.* 2019;42(Suppl 1):S90-S102.

72. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. JAMA*.* 2000;284(4):472-477.

73. Song IH, Zong J, Borland J, Jerva F, Wynne B, Zamek-Gliszczynski MJ, et al. The Effect of Dolutegravir on the Pharmacokinetics of Metformin in Healthy Subjects. J Acquir Immune Defic Syndr*.* 2016;72(4):400-407.

74. <https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf>. Tdpi. Accessed July 8, 2019.

75. Gervasoni C, Minisci D, Clementi E, Rizzardini G, Cattaneo D. How Relevant is the Interaction Between Dolutegravir and Metformin in Real Life? J Acquir Immune Defic Syndr*.* 2017;75(1):e24-e26.

76. May M, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. Ther Adv Endocrinol Metab*.* 2016;7(2):69-83.

77. Fichtenbaum CJ, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. Clin Pharmacokinet*.* 2002;41(14):1195-1211.

78. Han JH, Gordon K, Womack JA, Gibert CL, Leaf DA, Rimland D, et al. Comparative Effectiveness of Diabetic Oral Medications Among HIV-Infected and HIV-Uninfected Veterans. Diabetes Care*.* 2017;40(2):218-225.

79. Sutinen J, Hakkinen AM, Westerbacka J, Seppala-Lindroos A, Vehkavaara S, Halavaara J, et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy--a randomized double-blind placebo-controlled study. Antivir Ther*.* 2003;8(3):199-207.

80. Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, Grinspoon S. Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. Ann Intern Med*.* 2004;140(10):786-794.

81. Cavalcanti RB, Raboud J, Shen S, Kain KC, Cheung A, Walmsley S. A randomized, placebo-controlled trial of rosiglitazone for HIV-related lipoatrophy. J Infect Dis*.* 2007;195(12):1754-1761.

82. Grinspoon S. Use of thiazolidinediones in HIV-infected patients: what have we learned? J Infect Dis*.* 2007;195(12):1731-1733.

83. van Wijk JP, de Koning EJ, Cabezas MC, op't Roodt J, Joven J, Rabelink TJ, et al. Comparison of rosiglitazone and metformin for treating HIV lipodystrophy: a randomized trial. Ann Intern Med*.* 2005;143(5):337-346.

84. Pioglitazone - FDA label. <https://wwwaccessdatafdagov/drugsatfda_docs/label/2011/021073s043s044lblpdf>*.* Accessed July 10, 2019.

85. Makdissi A, Ghanim H, Vora M, Green K, Abuaysheh S, Chaudhuri A, et al. Sitagliptin exerts an antinflammatory action. J Clin Endocrinol Metab*.* 2012;97(9):3333-3341.

86. Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effects of sitagliptin therapy on markers of low-grade inflammation and cell adhesion molecules in patients with type 2 diabetes. Metabolism*.* 2014;63(9):1141-1148.

87. Goodwin SR, Reeds DN, Royal M, Struthers H, Laciny E, Yarasheski KE. Dipeptidyl peptidase IV inhibition does not adversely affect immune or virological status in HIV infected men and women: a pilot safety study. J Clin Endocrinol Metab*.* 2013;98(2):743-751.

88. Best C, Struthers H, Laciny E, Royal M, Reeds DN, Yarasheski KE. Sitagliptin Reduces Inflammation and Chronic Immune Cell Activation in HIV+ Adults With Impaired Glucose Tolerance. J Clin Endocrinol Metab*.* 2015;100(7):2621-2629.

89. Dube MP, Chan ES, Lake JE, Williams B, Kinslow J, Landay A, et al. A Randomized, Double-Blinded, Placebo-Controlled Trial of Sitagliptin for Reducing Inflammation and Immune Activation in Treated and Suppressed HIV Infection. Clin Infect Dis*.* 2018.

90. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med*.* 2016;375(4):311-322.

91. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med*.* 2016;375(19):1834-1844.

92. Diamant M, van Agtmael M. Liraglutide treatment in a patient with HIV and uncontrolled insulin-treated type 2 diabetes. Diabetes Care*.* 2012;35(5):e34.

93. Gutierrez AD, Balasubramanyam A. Dysregulation of glucose metabolism in HIV patients: epidemiology, mechanisms, and management. Endocrine*.* 2012;41(1):1-10.

94. Paik IJ, Kotler DP. The prevalence and pathogenesis of diabetes mellitus in treated HIV-infection. Best Pract Res Clin Endocrinol Metab*.* 2011;25(3):469-478.

95. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med*.* 2019;380(4):347-357.

96. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med*.* 2015;373(22):2117-2128.

96A. Feingold KR. Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes. 2022 Aug 26. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–97.

97. Garcia de Lucas MD, Olalla J. Experience of using ISGTL-2 in patients with DM2 and HIV infection. Eur J Intern Med*.* 2017;41:e29.

98. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier Gangrene Associated With Sodium-Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. Ann Intern Med*.* 2019.

99. Elem B, Ranjan P. Impact of immunodeficiency virus (HIV) on Fournier's gangrene: observations in Zambia. Ann R Coll Surg Engl*.* 1995;77(4):283-286.

100. Ngugi P, Magoha G, Nyaga P. Fournier's ganrene in the HIV era. Afr Health Sci*.* 2014;14(4):1063-1068.

101. Chazan B, Chen Y, Raz R, Kopelman D, Katz Z, Kniznik D, et al. Fournier's gangrene as the initial presentation of HIV infection. Int J Infect Dis*.* 2007;11(2):184-185.

102. Chalya PL, Igenge JZ, Mabula JB, Simbila S. Fournier's gangrene at a tertiary health facility in northwestern Tanzania: a single centre experiences with 84 patients. BMC Res Notes*.* 2015;8:481.

103. Saylor D. Neurologic Complications of Human Immunodeficiency Virus Infection. Continuum (Minneap Minn)*.* 2018;24(5, Neuroinfectious Disease):1397-1421.

104. Ghosh S, Chandran A, Jansen JP. Epidemiology of HIV-related neuropathy: a systematic literature review. AIDS Res Hum Retroviruses*.* 2012;28(1):36-48.

105. Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol*.* 1995;9(2):153-161.

106. Wang SX, Ho EL, Grill M, Lee E, Peterson J, Robertson K, et al. Peripheral neuropathy in primary HIV infection associates with systemic and central nervous system immune activation. J Acquir Immune Defic Syndr*.* 2014;66(3):303-310.

107. Erlandson KM, Zhang L, Ng DK, Althoff KN, Palella FJ, Jr., Kingsley LA, et al. Risk Factors for Falls, Falls With Injury, and Falls With Fracture Among Older Men With or at Risk of HIV Infection. J Acquir Immune Defic Syndr*.* 2019;81(4):e117-e126.

108. Ekrikpo UE, Kengne AP, Bello AK, Effa EE, Noubiap JJ, Salako BL, et al. Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. PLoS One*.* 2018;13(4):e0195443.

109. Palella FJ, Jr., Li X, Gupta SK, Estrella MM, Phair JP, Margolick JB, et al. Long-term kidney function, proteinuria, and associated risks among HIV-infected and uninfected men. AIDS*.* 2018;32(10):1247-1256.

110. Ng DK, Jacobson LP, Brown TT, Palella FJ, Jr., Martinson JJ, Bolan R, et al. HIV therapy, metabolic and cardiovascular health are associated with glomerular hyperfiltration among men with and without HIV infection. AIDS*.* 2014;28(3):377-386.

111. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol*.* 2017;28(4):1023-1039.

112. Wyatt CM, Arons RR, Klotman PE, Klotman ME. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. AIDS*.* 2006;20(4):561-565.

113. Naicker S, Aboud O, Gharbi MB. Epidemiology of acute kidney injury in Africa. Semin Nephrol*.* 2008;28(4):348-353.

114. Hou J, Nast CC. Changing concepts of HIV infection and renal disease. Curr Opin Nephrol Hypertens*.* 2018;27(3):144-152.

115. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS*.* 2012;26(7):867-875.

116. Mocroft A, Kirk O, Gatell J, Reiss P, Gargalianos P, Zilmer K, et al. Chronic renal failure among HIV-1-infected patients. AIDS*.* 2007;21(9):1119-1127.

117. Demirkaya N, Wit FW, van Den Berg TJ, Kooij KW, Prins M, Schlingemann RO, et al. HIV-Associated Neuroretinal Disorder in Patients With Well-Suppressed HIV-Infection: A Comparative Cohort Study. Invest Ophthalmol Vis Sci*.* 2016;57(3):1388-1397.

118. Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis*.* 2014;58(9):1308-1311.

119. Jabs DA, Drye L, Van Natta ML, Thorne JE, Holland GN, Studies of the Ocular Complications of ARG. Incidence and long-term outcomes of the human immunodeficiency virus neuroretinal disorder in patients with AIDS. Ophthalmology*.* 2015;122(4):760-768.

120. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab*.* 2007;92(7):2506-2512.

121. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis*.* 2010;201(3):318-330.

122. Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One*.* 2012;7(9):e44454.

123. Thompson-Paul AM, Lichtenstein KA, Armon C, Palella FJ, Jr., Skarbinski J, Chmiel JS, et al. Cardiovascular Disease Risk Prediction in the HIV Outpatient Study. Clin Infect Dis*.* 2016;63(11):1508-1516.

124. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol*.* 2019.

125. American Diabetes A. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2018. Diabetes Care*.* 2018;41(Suppl 1):S86-S104.

126. Suchindran S, Regan S, Meigs JB, Grinspoon SK, Triant VA. Aspirin Use for Primary and Secondary Prevention in Human Immunodeficiency Virus (HIV)-Infected and HIV-Uninfected Patients. Open Forum Infect Dis*.* 2014;1(3):ofu076.

127. Ladapo JA, Richards AK, DeWitt CM, Harawa NT, Shoptaw S, Cunningham WE, et al. Disparities in the Quality of Cardiovascular Care Between HIV-Infected Versus HIV-Uninfected Adults in the United States: A Cross-Sectional Study. J Am Heart Assoc*.* 2017;6(11).

128. Elf JL, Variava E, Chon S, Lebina L, Motlhaoleng K, Gupte N, et al. Prevalence and Correlates of Smoking Among People Living With HIV in South Africa. Nicotine Tob Res*.* 2018;20(9):1124-1131.

129. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med*.* 2015;162(5):335-344.

130. Xu Y, Chen X, Wang K. Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis. J Am Soc Hypertens*.* 2017;11(8):530-540.

131. Seaberg EC, Munoz A, Lu M, Detels R, Margolick JB, Riddler SA, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. AIDS*.* 2005;19(9):953-960.

132. American Diabetes A. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2019. Diabetes care*.* 2019;42(Suppl 1):S103-S123.

133. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab*.* 1992;74(5):1045-1052.

134. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, et al. Impact of HIV infection and HAART on serum lipids in men. JAMA*.* 2003;289(22):2978-2982.

134A. Grinspoon SK, Fitch KV, Zanni MV, Fichtenbaum CJ, Umbleja T, Aberg JA, Overton ET, Malvestutto CD, Bloomfield GS, Currier JS, Martinez E, Roa JC, Diggs MR, Fulda ES, Paradis K, Wiviott SD, Foldyna B, Looby SE, Desvigne-Nickens P, Alston-Smith B, Leon-Cruz J, McCallum S, Hoffmann U, Lu MT, Ribaudo HJ, Douglas PS; REPRIEVE Investigators. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. N Engl J Med. 2023 Aug 24;389(8):687-699.

135. Reddy KP, Parker RA, Losina E, Baggett TP, Paltiel AD, Rigotti NA, et al. Impact of Cigarette Smoking and Smoking Cessation on Life Expectancy Among People With HIV: A US-Based Modeling Study. J Infect Dis*.* 2016;214(11):1672-1681.

136. American Diabetes A. 5. Lifestyle Management: Standards of Medical Care in Diabetes-2019. Diabetes Care*.* 2019;42(Suppl 1):S46-S60.