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Diabetes in People with HIV

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Abstract

Purpose of Review: To discuss the diagnosis, treatment, and complications of diabetes in people with HIV (PWH) and to review HIV-related factors that may contribute to the development of diabetes or alter decisions in the care and treatment of PWH with diabetes.

Recent Findings: For those patients with atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, GLP-1 receptor agonists and SGLT-2 inhibitors should be considered for use. Evidence for this recommendation is, however, based on studies that were not conducted in populations consisting solely of PWH.

Summary: Diabetes is a significant comorbidity in PWH and adds to their already heightened risk of cardiovascular disease. HIV-specific factors, including interactions of antiretroviral therapy with medications that either treat diabetes and/or prevent cardiovascular disease, should be evaluated.

Keywords

HIV; antiretroviral therapy; diabetes; microvascular complications; macrovascular complications

Introduction

People with HIV (PWH) are living longer with advances in antiretroviral therapy (ART). As a result, PWH are at risk for diseases associated with aging, including diabetes. Diabetes is a cardiovascular (CV) disease risk factor and contributes to the already significant risk for developing CV disease among PWH. HIV care providers should recognize that each aspect of diabetes management, including diagnosis and therapy, may differ in PWH compared to a patient from the general population.

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Epidemiology of Diabetes

The prevalence of diabetes in a cohort in the United States of PWH on ≥ 6 months of ART has been reported to be 19.3% in women and 12.2% in men [1], similar to the prevalence seen in the general population [2]. Moreover, the prevalence of diabetes in general has steadily been increasing in low and middle income countries (LMIC), in part because of changes in diet, although HIV may also be a contributing factor [3]. The prevalence of diabetes in PWH in LMIC ranges from 1.3 to 18%. The wide range is in part because of different criteria used to define diabetes as well as actual differences in prevalence estimates among different populations [4].

Whether HIV infection itself is a risk factor for diabetes has not been clearly established and depends on the population studied. While there is some evidence that suggests HIV is associated with greater risk of diabetes [5,6], other studies have not demonstrated a direct association between HIV and diabetes [7,8]. Factors that could account for the discrepancy in these findings include different definitions of diabetes used in the studies.

Risk Factors

Several risk factors related to HIV place PWH at risk for developing diabetes. One such risk factor is ART. ART has evolved since the beginning of the HIV epidemic, and the effects of early ART differ from those of contemporary ART. In the early ART era, ART was associated with an increased incidence of diabetes, even after adjustment for body mass index (BMI) and age, as seen in the Multicenter AIDS Cohort Study, a prospective study of men with and without HIV. The majority of men with HIV on ART reported taking one or more protease inhibitors (PI), and the use of any PI was associated with diabetes incidence [5]. Also, both in the early and modern ART eras, ART has been associated with an increase in weight termed the “return to health” phenomenon [9].

Moreover, exposure to thymidine analogs, stavudine and zidovudine, has been associated with changes in fat distribution. Specifically, previous exposure to stavudine has been shown to be associated with greater pericardial adipose tissue volume [10], which is linked to greater risk for coronary artery disease events [11]. In addition, previous exposure to thymidine analogs is directly associated with greater visceral adipose tissue area [12] and reduced subcutaneous fat [13]. Of note, stavudine is not recommended by current guidelines [14], but previous stavudine exposure can remain a significant metabolic risk factor even after this medication is withdrawn [12].

However, the median BMI of PWH has been climbing over time. In the current era, ART is associated with increasing the risk of becoming overweight or obese [9,15].

Particular ART agents have been associated with weight gain. These include the integrase strand inhibitors (INSTIs), in particular dolutegravir, in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) tenofovir alafenamide (TAF) [16]. Certain patient populations are particularly susceptible to weight gain in the setting of INSTI use, including women, African Americans, and older PWH [9,16]. However, the effects of INSTIs and their associated weight gain on metabolic outcomes, including diabetes, is not yet known [9].

Diagnosis and Monitoring

For the general population, the American Diabetes Association (ADA) lists different methods to diagnose diabetes, including fasting glucose ≥ 126 mg/dl, 2 hour plasma glucose ≥ 200 mg/dl after a 75 gram oral glucose challenge, and hemoglobin A1c ≥ 6.5%. However, for specific patient populations, including PWH, the hemoglobin A1c may be inaccurate and is thus not a preferred method to diagnose diabetes. Hemoglobin A1c has been shown to underestimate glycemia in PWH, and abacavir has been associated with greater discordance between hemoglobin A1c and blood glucose [17]. As such, a plasma glucose based method is preferred [18].

Given the inaccuracy of hemoglobin A1c in PWH, fasting glucose is recommended for screening and should be obtained at the following time points: at the time of care initiation, when ART is started or changed, every 12 months and if clinically indicated. In the situation of a random glucose outside of the normal range, then a fasting glucose is recommended [14]. Similarly, the ADA recommends that plasma glucose based criteria, not hemoglobin A1c, should be used for the diagnosis of diabetes in PWH [18].

Treatment

Lifestyle interventions

Because of the lack of randomized controlled studies of interventions to treat diabetes in PWH, many recommendations for the treatment of diabetes are extrapolated from studies conducted in the general population.

Lifestyle interventions are recommended as the foundation of treatment in people with diabetes [19,20]. These include the following: tobacco product cessation, including e-cigarettes, nutrition therapy, and physical activity.

The ADA does not recommend a specific diet but does note that patients with diabetes should be referred to a registered dietitian. Moreover, the ADA recommends avoiding sugar sweetened beverages and emphasizes more whole foods over processed foods [20]. Similarly, the American Association of Clinical Endocrinology (AACE) recommends avoiding foods with sucrose or high amounts of fructose [19]. However, evidence has shown that PWH are more likely to have a lower quality diet, as measured by the Healthy Eating Index (HEI), than people without HIV [21]. As such, nutrition therapy represents an area that should be targeted in PWH in the treatment of diabetes.

Recommendations for physical activity in people with diabetes include ≥ 150 minutes of moderate intensity aerobic exercise over ≥ 3 days a week [20]. The American Heart Association recommends either 150 minutes of moderate intensity exercise a week or 75 minutes of vigorous intensity exercise a week [22], but the ADA notes that 75 minutes of vigorous intensity exercise a week may be adequate in younger and more physically able patients [20]. High quality data on the level of physical activity is sparse [23], but the available data suggests that PWH may not be achieving recommended levels of exercise

[24]. This underscores the importance for the clinician treating diabetes in PWH to address and discuss any barriers to exercise that the patient may have.

Metformin

Metformin is the first-line medication recommended in the treatment of type 2 diabetes by the ADA, if there is no contraindication to metformin use [25].

One consideration in the use of metformin in PWH is ART-metformin interactions. No adjustment to metformin is needed with use of NNRTIs, PIs, or nucleoside reverse transcriptase inhibitors (NRTIs) [14]. However, INSTI-metformin interactions exist, with the following INSTIs: bictegravir and dolutegravir, as both INSTIs can increase the area under the curve of metformin. As such, a maximum dose of metformin 1000 mg daily is recommended for use with dolutegravir, with a caveat to monitor for any adverse drug effects of metformin [14]. No specific maximum dose of metformin is noted in the package insert for bictegravir, as the magnitude of the interaction may not be clinically significant [26].

Thus, metformin can be considered as first-line therapy for PWH with diabetes, based on ADA guidelines, although monitoring for adverse effects from metformin and dose titration may be indicated in the setting of bictegravir and dolutegravir use, respectively.

Sulfonylureas

Sulfonylureas decrease A1c by 1–2%. Associated side effects include weight gain and hypoglycemia, and the risk of hypoglycemia with sulfonylurea use is increased in the setting of renal insufficiency. The ADA guidelines recommend considering the use of sulfonylureas as a second-line medication after metformin in patients with type 2 diabetes without ASCVD if cost of medication is a concern [25]. Sulfonylureas are relatively less expensive than other antihyperglycemic medications.

Among patients with diabetes with and without HIV who were naïve to diabetes medication, no difference in A1c change by HIV serostatus was observed in patients started on a sulfonylurea compared to A1c change in either patients started on metformin or a thiazolidinedione. Differences in side effect profile as a result of sulfonylurea treatment were not reported [27].

Specific considerations to note in the treatment of PWH is the adverse effect of weight gain with sulfonylurea use. A major point to consider is that the use of sulfonylureas in PWH should be measured against the fact that ART initiation is already a risk factor for weight gain.

No interactions between sulfonylureas and PIs, NNRTIs, NRTIs, or INSTIs have been reported [14].

Thiazolidinediones

Pioglitazone is a thiazolidinedione that is currently on the market and used in clinical practice. Compared to placebo, pioglitazone 30 mg daily lowers hemoglobin A1c by about

1% [28]. Adverse effects of pioglitazone include edema and an elevated risk of bone fractures in older individuals [29,30]. While some studies have described an association between pioglitazone and bladder cancer [31,32], others have not shown a significant relationship [33,34]. Pioglitazone carries a low risk of hypoglycemia [35] and has been associated with a reduction in ASCVD events in a general population study of individuals with type 2 diabetes and history of macrovascular disease [36].

The effect of pioglitazone on HIV-associated lipodystrophy syndrome (HALS) has been studied. HALS, which is associated with insulin resistance, is characterized by a redistribution in subcutaneous fat, including lipoatrophy in the face and extremities and lipoaccumulation in the neck, abdomen and trunk. HALS may also be associated with CV disease [37,38]. A risk factor for HALS includes use of thymidine analogs, a type of NRTI. [38]. In different studies, pioglitazone treatment has been shown to result in either no change or an increase in limb fat in patients with HALS . In addition, the effect of pioglitazone on insulin resistance, as measured by the homeostasis model assessment insulin resistance (HOMA-IR) or amended insulin-resistance ratio, in PWH has been shown to range from no change to a significant decrease in insulin resistance. Differences in these studies' findings may be secondary to differences in study duration, sample size, and study demographics [39–41].

DPP4 Inhibitors

DPP4 inhibitors lower hemoglobin A1c up to 0.8%, which is relatively less than the glucose lowering effect that is seen with GLP-1 receptor agonists, as discussed below [42,43]. This class of medications is not associated with hypoglycemia and is considered weight neutral. The DPP4 inhibitors have a favorable side effect profile, with nasopharyngitis being one of the most common adverse effects [44]. In placebo controlled trials of saxagliptin, upper respiratory tract infection was observed in 7.7% of participants in the treatment arm compared to 7.6% in the placebo arm [45]. The use of saxagliptin concurrently with the INSTI elvitegravir and cobicistat may potentially result in an increase in saxagliptin concentration [14].

DPP4 is a cell-surface protease which inactivates incretins, which explains the glucose lowering effect of DPP4 inhibitors. In addition, DPP4 is involved with T cell activation, and DPP4 or CD26 on lymphocytes also binds to the HIV associated protein gp120 [46]. The question of whether DPP4 inhibitors affect the immune system in PWH has been of interest. In a pilot study of PWH on ART and without diabetes randomized either to sitagliptin or placebo, no significant change in CD4+ T cell count was associated with sitagliptin use [47].

In clinical studies, DPP4 inhibitors have shown to exert an anti-inflammatory effect [48,49]. In a study of PWH, a randomized, controlled trial studied whether 16 weeks of sitagliptin treatment decreased soluble CD14, a monocyte activation marker. No significant change in soluble CD14 was noted from baseline to the end of the study, although it was well tolerated [50].

In summary, DPP4 inhibitors can be considered in the treatment of diabetes in PWH after taking into account any potential ART interaction.

GLP-1 Receptor Agonists

The ADA recommends the use of a GLP-1 receptor agonist, in addition to metformin, in those patients with type 2 diabetes and ASCVD [25]. This recommendation is the result of several CV outcomes trials that have shown the benefit in this class of medications in reducing ASCVD risk. The AACE recommends GLP-1 receptor agonist therapy in those patients with type 2 diabetes and ASCVD or with high risk of ASCVD, independent of glycemic control [19]. Adverse effects associated with GLP-1 receptor agonist treatment include nausea and vomiting. No causal association between GLP-1 receptor agonist treatment and pancreatitis has been demonstrated [51].

In the LEADER trial of participants with type 2 diabetes, treatment with liraglutide, a once daily GLP-1 receptor agonist, was associated with a reduction in the composite primary endpoint of non-fatal myocardial infarction, non-fatal stroke, and CV-related death [52]. Similar results were seen in separate studies of dulaglutide, albiglutide (no longer on the market), and injectable semaglutide. Semaglutide, in particular, was associated with a reduction in non-fatal MI [53].

In 2 case studies, liraglutide resulted in weight loss and improvements in hemoglobin A1c and fasting glucose in PWH [54,55]. No guidelines recommend the use of GLP-1 receptor agonists specifically in PWH because to date there are no randomized controlled trials of GLP-1 receptor agonists in PWH. However, given the increased risk of ASCVD in PWH and weight loss associated with this class of medications, GLP-1 receptor agonists are an attractive agent to consider in the treatment of diabetes in PWH. As such, despite the lack of specific guidelines addressing this issue, the atheroprotective nature of GLP-1 receptor agonists reflect favorably on these medications, in the goal to reduce ASCVD risk in PWH.

SGLT-2 Inhibitors

Similar to GLP-1 receptor agonists, SGLT-2 inhibitors are recommended in the treatment of patients with type 2 diabetes and ASCVD, specifically chronic kidney disease and/or congestive heart failure, by the ADA [25]. This class of medications is associated with weight loss.

Several CV outcomes trials have demonstrated the benefit of this class of medications in patients with ASCVD. In the EMPA-REG trial, empagliflozin was associated with a reduced risk of the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and CV-related death [56]. Similar results were noted in separate trials of dapagliflozin [57] and canagliflozin [58]. Canagliflozin and dapaglifozin each have a Food and Drug Administration approved indication for lowering the risk of hospitalization for heart failure [59], and canagliflozin has also been shown to lower the risk of the composite renal outcome of end-stage kidney disease, doubling of serum creatinine or renal or CV death [60]. Adverse effects to consider with SGLT-2 inhibitors include the following: increased risk of diabetic ketoacidosis in patients with type 1 diabetes or those prone to diabetic ketoacidosis and genital mycotic infections in men and women. Additional reported adverse effects include necrotizing fasciitis of the perineum and urinary tract infections [59]. In an observational study of PWH and type 2 diabetes treated with canagliflozin, treatment

resulted in both a decreased median BMI (−2.01 kg/m^2) and median fasting glucose (−42.12 mg/dL) [61].

In a study by Garcia de Lucas *et al*, 8 patients with HIV on ART and with diabetes were treated with canagliflozin, starting at 100 mg daily and increased to 300 mg daily, for 24 weeks. At the end of the study, significant improvements in weight (−6.12 kg) and glycemic control (−42.12 mg/dl in fasting glucose) were observed, compared to baseline levels. None of the patients discontinued canagliflozin or required changes to ART [61].

In summary, the benefits of SGLT-2 inhibitors with regards to ASCVD risk reduction should be weighed against possible adverse effects in the care of PWH.

Insulin

The ADA recommends the use of insulin for patients 1) with a hemoglobin A1c > 10% or blood glucose ≥ 300 mg/dL, 2) symptoms of catabolism, or 3) symptoms of hyperglycemia. Basal insulin can be initiated at a dose of 10 units daily or 0.1–0.2 units/kilogram daily. Some patients may be candidates for dose titration of basal insulin, for example, to increase basal insulin by 2 units every 3 days until a goal fasting glucose target is met.

If basal insulin has been titrated to an optimal dose and a patient's glycemic target overall is not met, then prandial insulin can be started, usually once daily with the patient's largest meal of the day. Additional prandial doses, up to 3 doses total a day, can be added subsequently to achieve a goal glycemic target. Alternately, for those patients who are unable to or do not want to take multiple injections of insulin daily, pre-mixed insulin administered twice daily is an option. Disadvantages of insulin therapy include hypoglycemia, weight gain [25], and a narrow therapeutic index [62].

Sequence of initiating agents for the treatment of diabetes

As noted above, the ADA recommends metformin as the first-line agent to treat diabetes, in addition to healthy lifestyle interventions [25]. The AACE also recommends metformin as a preferred first-line agent, although a GLP-1 receptor agonist or SGLT-2 inhibitor may be considered instead of metformin in patients with chronic kidney disease or ASCVD or at high risk for ASCVD [63]. After metformin monotherapy, the ADA's therapy decision making-tree assesses the presence or absence of ASCVD, chronic kidney disease, or heart failure. If ASCVD, chronic kidney disease, or heart failure is present, then a GLP-1 receptor agonist or SGLT-2 inhibitor is recommended, regardless of glycemic status. If ASCVD, chronic kidney disease, or heart failure is absent, then subsequent add-on therapy should take into consideration issues including cost of medication, the need for weight loss, and risk of hypoglycemia. The recommendations then note that a hemoglobin A1c should be obtained every 3–6 months to re-assess the need for additional therapy [25], although as noted above, hemoglobin A1c may not be accurate in PWH. For example, in a patient with HIV, for whom cost of medications is a concern and who does not have ASCVD, chronic kidney disease, or heart failure, an appropriate sequence of starting medications may be as follows: 1) metformin and lifestyle interventions, 2) sulfonylurea, 3) thiazolidinedione, and 4) basal insulin, after taking into account contraindications to these medications and the patient's preferences.

Diabetes-Related Complications

Peripheral Neuropathy

There are several HIV-associated neuropathies, including the most common, HIV-associated distal symmetric polyneuropathy (HIV-DSP). Risk factors include age and exposure to d4T [64], which is no longer recommended for use [14].

Distal symmetric peripheral neuropathy is also a known microvascular complication from diabetes. The ADA recommends an annual comprehensive foot examination in all patients with diabetes. In those patients with diabetes and known peripheral neuropathy and/or history of foot ulcer or amputation, the ADA recommends a foot examination at each visit. Such an examination involves 1) a detailed history, 2) visual inspection, 3) a neurologic assessment and 4) a vascular assessment of the feet [65]. As such, the clinician caring for PWH who have diabetes should consider both HIV-DSP and peripheral neuropathy secondary to diabetes as etiologies for peripheral neuropathy in patients. A referral to podiatry is recommended for those patients with foot wounds or ulcers.[65]

Retinopathy

Because of an aging general population, the prevalence of visual impairment is predicted to increase in the United States in the next 30 years, and a major cause of this is diabetic retinopathy [66]. The ADA recommends a dilated eye examination in patients with type 2 diabetes at the time of diabetes diagnosis [65]. Although opportunistic infection of the retina (CMV retinitis) was once common in PWH in the pre-ART era, its incidence of this has decreased markedly with the widespread availability of ART [67,68].

Kidney Disease

Diabetic kidney disease and nephropathy, which includes proteinuria, hypertension, and reduced renal function, are seen in patients with diabetes, can have multiple etiologies, and is the main cause of end-stage renal disease in the United States [69]. In addition, both HIV infection and some ART are associated with kidney disease, and the kidney diseases associated with HIV infection have changed over the course of the HIV epidemic. For example, HIV-associated nephropathy was more prevalent in the United States prior to the ART era. With effective ART, PWH are living longer and are experiencing more age-related kidney diseases, including diabetic nephropathy. In addition, tenofovir disoproxil fumarate (TDF) has been associated with renal tubular dysfunction and chronic kidney disease [70]. It should be noted that proteinuria is associated with HIV status, even in those without diabetes and may be related to systemic inflammation [71].

To screen for kidney disease in PWH before and after ART initiation, current guidelines recommend obtaining 1) a basic chemistry and urinalysis at the start of care and at the time of ART initiation, 2) a basic chemistry alone 2 to 8 weeks after ART initiation, every 6 months, and if clinically indicated, and 3) a urinalysis every 6 months if on TDF or every 12 months and if clinically indicated [14]. The ADA recommends obtaining a urine microalbumin to creatinine ratio and an estimated glomerular filtration rate yearly in patients with type 2 diabetes [65].

Macrovascular disease

CV disease is a major cause of mortality in people with diabetes [72]. In addition, PWH have a greater risk for developing CV disease compared to the general population. CV risk factors, both traditional, including diabetes, and non-traditional, including inflammation, are seen in PWH.

The American College of Cardiology (ACC) considers HIV infection to be a risk-enhancing clinical factor that should be taken into account when determining a patient's CV risk. For example, if a patient with HIV is found to have an intermediate 10 year of CV disease (≥ 7.5% to < 20%) using the Pooled Cohort Equations calculator, the knowledge that HIV infection is a risk-enhancing factor can better inform the join decision between clinician and patient to start a moderate intensity statin.

As noted above, a mainstay of primary CV disease prevention is statin therapy. However, no trial data specifically focused on statins and their effect on primary prevention in PWH have been published to date. The ongoing prospective REPRIEVE study was designed to answer this question, i.e., the effect of pitavastatin on primary CV disease prevention in PWH, and is ongoing [73]. Statin-ART interactions should also be taken into consideration in the patient-clinician decision to initiate statin therapy. For example, with regards to protease inhibitor (PI) use, atorvastatin should not exceed 20 mg daily when administered with the PI darunavir and the pharmacokinetic enhancer cobicistat (DRV/c). No dose adjustment is needed with pitavastatin in co-administration with PIs, NNRTIs, or INSTIs [14].

In summary, both diabetes and HIV infection are CV disease risk factors. Although no published randomized trials have focused on statin use and primary CV disease prevention in PWH, current recommendations based on general population studies note that statin use is indicated in those patients at high risk for CV disease and should be considered in those at intermediate risk and with a risk enhancer present.

Conclusions

Each aspect of diabetes care in PWH is distinct from diabetes care in the general population. In the screening and diagnosis of diabetes in PWH, hemoglobin A1c should be avoided as it is an inaccurate measurement in PWH, and plasma glucose measurements should be used instead. Anti-diabetes medications should be initiated and adjusted based on the type of ART a patient is taking because of potential interactions with ART. The use of general population CV risk calculators do not include HIV infection as a risk factor, which should be taken into consideration in the decision to start a statin. Finally, PWH are at risk for microvascular complications that can also be seen in the context of diabetes so appropriate surveillance is warranted.

References

1. Buchacz K, Baker RK, Palella FJ, et al. Disparities in prevalence of key chronic diseases by gender and race/ethnicity among antiretroviral-treated HIV-infected adults in the US. Antivir Ther. 2013;18(1):65–75. [PubMed: 23111762]

2. Warriner AH, Burkholder GA, Overton ET. HIV-Related Metabolic Comorbidities in the Current ART Era. Infect Dis Clin N Am. 2014;28(3):457–+.
3. Noubissi EC, Katte JC, Sobngwi E. Diabetes and HIV. Curr Diabetes Rep. 2018;18(11).
4. Patel P, Rose CE, Collins PY, et al. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: a systematic review and meta-analysis. Aids. 2018;32:S5–S20. [PubMed: 29952786]
5. Brown TT, Cole SR, Li XH, 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. [PubMed: 15911733]
6. Galli L, Salpietro S, Pellicciotta G, et al. Risk of type 2 diabetes among HIV-infected and healthy subjects in Italy. European journal of epidemiology. 2012;27(8):657–665. [PubMed: 22722952]
7. Prioreschi A, Munthali RJ, Soepnel L, et al. Incidence and prevalence of type 2 diabetes mellitus with HIV infection in Africa: a systematic review and meta-analysis. BMJ open. 2017;7(3):e013953.
8. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al. HIV infection and the risk of diabetes mellitus. Aids. 2009;23(10):1227–1234. [PubMed: 19444074]
9. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis. 2020;33(1):10–19. [PubMed: 31789693]
10. Knudsen AD, Krebs-Demmer L, Bjørge NID, et al. Pericardial Adipose Tissue Volume Is Independently Associated With Human Immunodeficiency Virus Status and Prior Use of Stavudine, Didanosine, or Indinavir. The Journal of infectious diseases. 2020;222(1):54–61. [PubMed: 32027374]
11. Antonopoulos AS, Antoniades C. The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles. The Journal of physiology. 2017;595(12):3907–3917. [PubMed: 28191635]
12. Gelpi M, Afzal S, Fuchs A, et al. Prior exposure to thymidine analogs and didanosine is associated with long-lasting alterations in adipose tissue distribution and cardiovascular risk factors. Aids. 2019;33(4):675–683. [PubMed: 30585844]
13. Mallon PW, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. Aids. 2003;17(7):971–979. [PubMed: 12700446]
14. https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf. Accessed (October 3, 2020). PoAGfAaAGftUoAAiAaAwHDoHaHSAa.
15. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(6):1379–1389.
16. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. New Engl J Med. 2019;381(9):803–815. [PubMed: 31339677]
17. Kim PS, Woods C, Georgoff P, et al. A1C Underestimates Glycemia in HIV Infection. Diabetes Care. 2009;32(9):1591–1593. [PubMed: 19502538]
18. Assoc AD. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43:S14–S31. [PubMed: 31862745]
19. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm-2020 Executive Summary. Endocr Pract. 2020;26(1):107–139. [PubMed: 32022600]
20. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S48–s65. [PubMed: 31862748]
21. Weiss JJ, Sanchez L, Hubbard J, Lo J, Grinspoon SK, Fitch KV. Diet Quality Is Low and Differs by Sex in People with HIV. The Journal of nutrition. 2019;149(1):78–87. [PubMed: 30624677]
22. Arnett DK, Khera A, Blumenthal RS. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Part 1, Lifestyle and Behavioral Factors. Jama Cardiol. 2019;4(10):1043–1044. [PubMed: 31365022]

23. Schuelter-Trevisol F, Wolff FH, Alencastro PR, et al. Physical activity: do patients infected with HIV practice? How much? A systematic review. Current HIV research. 2012;10(6):487–497. [PubMed: 22762420]
24. Vancampfort D, Mugisha J, Richards J, De Hert M, Probst M, Stubbs B. Physical activity correlates in people living with HIV/AIDS: a systematic review of 45 studies. Disability and rehabilitation. 2018;40(14):1618–1629. [PubMed: 28325087]
25. Assoc AD. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020 (vol 43, pg S98, 2020). Diabetes Care. 2020;43(8):1979–1979. [PubMed: 32503835]
26. Custodio J, West S, Yu A, et al. Lack of Clinically Relevant Effect of Bictegravir (BIC, B) on Metformin (MET) Pharmacokinetics (PK) and Pharmacodynamics (PD). Open forum infectious diseases. 2017;4(Suppl 1):S429.
27. Han JH, Gordon K, Womack JA, et al. Comparative Effectiveness of Diabetic Oral Medications Among HIV-Infected and HIV-Uninfected Veterans. Diabetes Care. 2017;40(2):218–225. [PubMed: 27634393]
28. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010;33(8):1859–1864. [PubMed: 20484130]
29. Viscoli CM, Inzucchi SE, Young LH, et al. Pioglitazone and Risk for Bone Fracture: Safety Data From a Randomized Clinical Trial. The Journal of clinical endocrinology and metabolism. 2017;102(3):914–922. [PubMed: 27935736]
30. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione use and bone loss in older diabetic adults. The Journal of clinical endocrinology and metabolism. 2006;91(9):3349–3354. [PubMed: 16608888]
31. Ferwana M, Firwana B, Hasan R, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. Diabetic medicine : a journal of the British Diabetic Association. 2013;30(9):1026–1032. [PubMed: 23350856]
32. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. BMJ (Clinical research ed). 2016;352:i1541.
33. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes. Jama. 2015;314(3):265–277. [PubMed: 26197187]
34. Filipova E, Uzunova K, Kalinov K, Vekov T. Pioglitazone and the Risk of Bladder Cancer: A Meta-Analysis. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2017;8(4):705–726.
35. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–795. [PubMed: 19336687]
36. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279–1289. [PubMed: 16214598]
37. Maggi P, Di Biagio A, Rusconi S, et al. Cardiovascular risk and dyslipidemia among persons living with HIV: a review. Bmc Infect Dis. 2017;17.
38. Koutkia P, Grinspoon S. HIV-associated lipodystrophy: pathogenesis, prognosis, treatment, and controversies. Annual review of medicine. 2004;55:303–317.
39. Yarasheski KE, Cade WT, Overton ET, et al. Exercise training augments the peripheral insulin-sensitizing effects of pioglitazone in HIV-infected adults with insulin resistance and central adiposity. American journal of physiology Endocrinology and metabolism. 2011;300(1):E243–251. [PubMed: 20959530]
40. Slama L, Lanoy E, Valantin MA, et al. Effect of pioglitazone on HIV-1-related lipodystrophy: a randomized double-blind placebo-controlled trial (ANRS 113). Antivir Ther. 2008;13(1):67–76. [PubMed: 18389900]
41. Calmy A, Hirschel B, Hans D, Karsegard VL, Meier CA. Glitazones in lipodystrophy syndrome induced by highly active antiretroviral therapy. Aids. 2003;17(5):770–772. [PubMed: 12646807]

42. Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, Barranco RJ, Umpierrez GE. Safety and Efficacy of DPP4 Inhibitor and Basal Insulin in Type 2 Diabetes: An Updated Review and Challenging Clinical Scenarios. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2018;9(5):1775–1789.
43. Hinnen D Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes spectrum : a publication of the American Diabetes Association. 2017;30(3):202–210. [PubMed: 28848315]
44. Gallwitz B Clinical Use of DPP-4 Inhibitors. Frontiers in endocrinology. 2019;10:389. [PubMed: 31275246]
45. Onglyza (saxagliptin) - FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022350lbl.pdf. Accessed November 30.
46. Lambeir AM, Durinx C, Scharpé S, De Meester I. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV. Critical reviews in clinical laboratory sciences. 2003;40(3):209–294. [PubMed: 12892317]
47. 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. The Journal of clinical endocrinology and metabolism. 2013;98(2):743–751. [PubMed: 23264399]
48. Makdissi A, Ghanim H, Vora M, et al. Sitagliptin exerts an antinflammatory action. The Journal of clinical endocrinology and metabolism. 2012;97(9):3333–3341. [PubMed: 22745245]
49. 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: clinical and experimental. 2014;63(9):1141–1148. [PubMed: 25034387]
50. Dube MP, Chan ES, Lake JE, et al. A Randomized, Double-blinded, Placebo-controlled Trial of Sitagliptin for Reducing Inflammation and Immune Activation in Treated and Suppressed Human Immunodeficiency Virus Infection. Clinical Infectious Diseases. 2019;69(7):1165–1172. [PubMed: 30535188]
51. Aroda VR. A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. Diabetes, obesity & metabolism. 2018;20 Suppl 1:22–33.
52. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine. 2016;375(4):311–322. [PubMed: 27295427]
53. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England journal of medicine. 2016;375(19):1834–1844. [PubMed: 27633186]
54. 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. [PubMed: 22517942]
55. García de Lucas MD, Olalla Sierra J, Piña Fernández J. Liraglutide treatment in a patient with HIV, type 2 diabetes and sleep apnoea-hypopnoea syndrome. Diabetes & metabolism. 2015;41(1):102–103. [PubMed: 25455831]
56. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine. 2015;373(22):2117–2128. [PubMed: 26378978]
57. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine. 2019;380(4):347–357. [PubMed: 30415602]
58. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England journal of medicine. 2017;377(7):644–657. [PubMed: 28605608]
59. Das SR, Everett BM, Birtcher KK, et al. 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020;76(9):1117–1145. [PubMed: 32771263]
60. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England journal of medicine. 2019;380(24):2295–2306. [PubMed: 30990260]

61. García de Lucas MD, Olalla J. Experience of using ISGTL-2 in patients with DM2 and HIV infection. European journal of internal medicine. 2017;41:e29. [PubMed: 28318649]
62. Kaarsholm NC, Lin S, Yan L, et al. Engineering Glucose Responsiveness Into Insulin. Diabetes. 2018;67(2):299–308. [PubMed: 29097375]
63. Garber AJ, Handelsman Y, Grunberger G, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY. Endocr Pract. 2020;26(1):107–139. [PubMed: 32022600]
64. Kaku M, Simpson DM. HIV neuropathy. Curr Opin Hiv Aids. 2014;9(6):521–526. [PubMed: 25275705]
65. Assoc AD. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43:S135–S151. [PubMed: 31862754]
66. “Burden of Vision Loss.” https://www.cdc.gov/visionhealth/risk/burden.htm. Accessed October 2.
67. Skiest DJ. Cytomegalovirus retinitis in the era of highly active antiretroviral therapy (HAART). Am J Med Sci. 1999;317(5):318–335. [PubMed: 10334120]
68. Goldberg DE, Smithen LM, Angelilli A, Freeman WR. HIV-associated retinopathy in the HAART era. Retina-J Ret Vit Dis. 2005;25(5):633–649.
69. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. Am J Kidney Dis. 2018;71(6):884–895. [PubMed: 29398179]
70. Cohen SD, Kopp JB, Kimmel PL. Kidney Diseases Associated with Human Immunodeficiency Virus Infection. New Engl J Med. 2017;377(24):2363–2374. [PubMed: 29236630]
71. Palella FJ Jr., Li X, Gupta SK, et al. Long-term kidney function, proteinuria, and associated risks among HIV-infected and uninfected men. Aids. 2018;32(10):1247–1256. [PubMed: 29561293]
72. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S111–s134. [PubMed: 31862753]
73. Grinspoon SK, Fitch KV, Overton ET, et al. Rationale and design of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). Am Heart J. 2019;212:23–35. [PubMed: 30928825]