Diagnosing and Managing Diabetes in HIV-Infected Patients: Current Concepts

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Diabetes mellitus (DM) is a common condition with significant associated morbidity and mortality. DM diagnosis and management among human immunodeficiency virus (HIV)-infected patients is a particularly relevant topic as the HIV-infected population ages and more HIV-infected individuals live with chronic medical comorbidities. Although there is mixed evidence regarding HIV as an independent risk factor for DM, multiple factors related to HIV and its treatment are associated with DM. This review covers the epidemiology of DM in HIV-infected patients, and diagnosis, management, and treatment goals for DM in HIV-infected patients. We highlight the most recent DM treatment guidelines from the American Diabetes Association and the European Association for the Study of Diabetes, emphasizing individualization of DM medication therapy and treatment goals. Finally, we review a comprehensive approach to cardiovascular disease risk reduction in HIV-infected patients with DM and measures to prevent other complications of DM.

Keywords. HIV; diabetes mellitus; CVD.

Diabetes mellitus (DM) is a common condition, affecting 8.5% of the US population [1], with DM prevalence estimates in human immunodeficiency virus (HIV)-infected patients of up to 14% [2]. DM is a leading cause of cardiovascular disease (CVD), blindness, end-stage renal disease, amputations, and hospitalizations.

The goals of this review are to update clinicians on the diagnosis and management of DM in HIV-infected patients, with detailed discussion of treatment goals and CVD risk reduction. Although the management of DM in HIV-infected patients follows the same general guidelines as in HIV-uninfected patients, there are specific considerations with respect to the use of hemoglobin A1c (HbA1c) testing in HIV-infected individuals and

the interactions of particular medications with antiretroviral therapy (ART).

EPIDEMIOLOGY OF DM IN HIV-INFECTED PATIENTS

The prevalence of DM in HIV-infected patients has been reported to range from 2% to 14% and varies by the composition of the cohort studied, how DM diagnosis is ascertained, and how DM risk factors are accounted for in the analysis [2–5]. There is conflicting evidence on whether HIV infection is an independent risk factor for DM, with some studies showing increased risk [2, 6, 7] and others showing no independent effect of HIV on DM or showing an inverse effect [4, 8, 9].

Despite the conflicting evidence on the independent role of HIV in DM, certain factors are clearly associated with DM, including increasing age, obesity, and genetic factors. Other factors influence DM incidence in the general population but are more common in HIV-infected patients: hepatitis C virus infection [10], use of certain medications (atypical antipsychotics, corticosteroids), opiate use, and low testosterone [11]. Furthermore, ART-associated lipoatrophy [4] and visceral fat

accumulation/lipohypertrophy [3, 12] and HIV-related inflammation (increased proinflammatory cytokines and/or free fatty acids) [13, 14] are DM risk factors in HIV-infected patients. For additional information regarding etiology of DM in HIV-infected patients, readers are referred to a comprehensive article [15].

EFFECTS OF SPECIFIC MEDICATIONS ON DM RISK

Antiretroviral Therapy
Preclinical studies demonstrate that protease inhibitors (PIs) increase insulin resistance through effects on the GLUT-4 transporter and decrease insulin secretion through effects on β-cell function, but the clinical impact of these changes is unclear [16]. It is clear, however, that exposure to certain first-generation ART agents, such as stavudine and indinavir, is strongly associated with developing DM. Use of these agents peaked in 1997–1998 and decreased through 2007–2009. Reflecting this, one study revealed DM incidence peaking in 1999–2000 at 23.2 per 1000 person-years of follow-up (PYFU) and decreasing thereafter to the current level of 5 per 1000 PYFU [17]. A head-to-head comparison of currently prescribed ART regimens revealed that efavirenz increased glucose to a greater degree than atazanavir, although the difference was small (about 4 mg/dL) [18], and the overall effect of current ART on glucose metabolism is modest in most patients.

Statins
Statins are commonly used in HIV-infected patients and can increase insulin resistance and DM [19], although results in studies of HIV-infected patients have been mixed [20–22]. Given the cardiovascular (CV) event reduction benefit from statins, increases in insulin resistance/DM likely do not outweigh the benefit of statin therapy in the general population or in HIV-infected patients [23, 24].

DIABETES DIAGNOSIS

Diabetes and Prediabetes Definitions
Table 1 shows the current American Diabetes Association (ADA) definitions of DM and prediabetes [25].

Use of HbA1c in HIV-Infected Patients
HbA1c is the percentage of glycated hemoglobin and reflects long-term glucose status. In conditions associated with shortened red blood cell lifespan, such as hemolytic anemia and pregnancy, only fasting plasma glucose (FPG) or oral glucose tolerance testing should be used to diagnose DM [25, 26]. Data are accumulating that HbA1c may underestimate glycemia in HIV-infected individuals. Although the degree of discordance has varied, higher mean corpuscular volume, nucleoside reverse transcriptase inhibitor use (specifically abacavir), and lower CD4 count have been associated with discordance [27–31].

Testing Recommendations
In view of the possible discordance between HbA1c and glycemic control, we believe it would be prudent to use FPG for the diagnosis of DM, particularly in patients who have risk factors for HbA1c inaccuracy [32]. We agree with the Department of Health and Human Services guidelines that FPG testing should be performed every 6–12 months in all HIV-infected patients and clinicians should consider testing 1–3 months after starting ART [33].

PREVENTING DIABETES

Although a detailed review of DM prevention is beyond the scope of this article, readers are referred to the Standards of Medical Care in Diabetes for DM prevention guidelines (page S20; available at: http://care.diabetesjournals.org/content/37/Supplement_1/S14.extract). Practical implementation of these guidelines may be achieved through community-based options, such as the evidence-based Young Men's Christian Association DM prevention program (Available at: http://www.ymca.net/diabetes-prevention/).

DIABETES MANAGEMENT

New Guidelines Focused on Individual Management
The current guidelines for DM management released by the ADA and the European Association for the Study of Diabetes in 2012 emphasize a patient-centered approach in which recommendations are "based on the needs, preferences, and tolerances

Table 1. Definitions of Prediabetes and Diabetes[a]

	Hemoglobin A1c[b]	Fasting Plasma Glucose	Random Plasma Glucose	Oral Glucose Tolerance Test
Diabetes	≥6.5%	≥126 mg/dL (≥7.0 mmol/L)	≥200 mg/dL (≥11.1 mmol/L) with polyuria and polydipsia	≥200 mg/dL (≥11.1 mmol/L)
Prediabetes	5.7%–6.4%	100–125 mg/dL (5.6–6.9 mmol/L)	. . .	140–199 mg/dL (7.8–11.1 mmol/L)
Normal	<5.7%	≤99 mg/dL (≤5.5 mmol/L)	. . .	≤139 mg/dL (≤7.7 mmol/L)

[a] All laboratory values should be confirmed with repeat testing.

[b] Hemoglobin A1c may be inaccurate in the setting of human immunodeficiency virus, so it is not recommended by these authors for diabetes diagnosis.

of each patient" [34]. Because there is a dearth of head-to-head trials of second-line DM medications, management decisions depend on both the preferences of the patient and the desired clinical outcomes.

Initial Management

Lifestyle modification can have a meaningful impact on glucose control and the course of DM. Referral to a registered dietician for medical nutrition therapy is recommended for all patients with DM [25], as even modest weight loss (as little as 2 kg) can have an impact on glycemic control [35, 36]. Additionally, moderate-intensity aerobic physical activity is recommended for adults with DM [25].

Switching Art Regimens

Switching ART regimens should be considered if a patient is on lopinavir/ritonavir or a thymidine analogue (zidovudine, stavudine) [37]; however, switching other medications is of uncertain benefit.

Diet Recommendations

The American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society guidelines for management of overweight and obesity in adults recommend a reduced-calorie intake diet as part of a comprehensive lifestyle modification intervention [38]. Calorie guidelines for weight loss are (1) 1200–1500 calories/day for women or 1500–1800 calories/day for men; (2) an energy deficit of 500 or 750 calories per day, based on the individual; or (3) an evidence-based diet that restricts a certain food type (eg, high-carbohydrate foods) to create an energy deficit. Dietary recommendations for patients with DM include monitoring carbohydrate intake, limiting consumption of sugar-sweetened beverages, and following a Mediterranean-style diet [25]. A patient-friendly diet guide is available at (http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/)

Exercise Recommendations

Aerobic exercise is recommended for at least 150 minutes a week, spread out over at least 3 days per week, along with strength training twice a week. Clinicians can recommend several strategies to increase physical activity among their patients [39–43]: an exercise partner, use of a pedometer with a target (eg, 10 000 steps/day), or individualized counseling with exercise prescription. Linking patients with community- or workplace-based programs may increase exercise uptake.

Medication Therapy

If glucose control is not optimized with lifestyle modification alone, medication therapy should be initiated. Table 2 provides a summary of DM medications highlighting special considerations in HIV-infected patients.

Metformin

The first-line medication for DM is metformin. Advantages to metformin include an average 1% decline in HbA1c, a long track record of safety and efficacy data, no hypoglycemia when given alone, no weight gain, and low cost (generic). Additionally, there may be an independent CVD risk reduction benefit to metformin [44]. Disadvantages include gastrointestinal side effects, particularly nausea and diarrhea, which can be minimized by prescribing a low dose and titrating up. Another rare side effect is lactic acidosis. The contraindications to metformin reflect the associated increased risk of lactic acidosis: chronic kidney disease with creatinine >1.4 mg/dL in women and >1.5 mg/dL in men, hypoxia, decompensated liver disease, severe congestive heart failure (CHF), alcohol abuse, and past history of lactic acidosis (unless there is a remote history specifically related to stavudine or didanosine without recurrence). Special caution should be used when metformin is coadministered with dolutegravir, as dolutegravir increases metformin concentration [45].

Second-line Treatments

After lifestyle modification and metformin, if a patient is still not at goal, there are multiple treatment options.

Sulfonylureas

Sulfonylureas (eg, glipizide and glyburide) act by stimulating insulin release from pancreatic β-cells. Advantages of sulfonylureas include a 1% HbA1c decrease, a long track record of safety and efficacy data, proven decreases in microvascular events, and relatively low cost (generic). Disadvantages include weight gain (2–4 kg), hypoglycemia due to the mechanism of action, and high failure rate (ie, a short time of control on sulfonylurea before additional therapy is required).

Thiazolidinediones

The thiazolidinediones (rosiglitazone and pioglitazone) work by improving target cell response to insulin, thereby lowering glucose. The advantages of thiazolidinedione treatment are a 1% HbA1c decrease and no hypoglycemia. There is a potential independent CVD risk reduction benefit of pioglitazone [46], and pioglitazone raises high-density lipoprotein, lowers triglycerides, and decreases liver fat [47]. There is a low failure rate of thiazolidinediones compared with sulfonylureas, and a modest beneficial effect on lipoatrophy may be achieved [48]. Disadvantages include high cost (no generic formulation available), weight gain, fluid retention, and worsening CHF (including in patients with diastolic dysfunction), macular edema, osteoporosis/fracture, and possibly increased risk of bladder cancer [49, 50]. Sales of rosiglitazone were previously restricted due to concern for increased cardiovascular events, however, after US Food and Drug Administration review, the restrictions were removed in mid-2013.

Table 2. Oral Diabetes Medications With Special Considerations in HIV

Class	Mechanism	Generic Name	Brand Name	Special Considerations in HIV
Biguanides	• Decrease hepatic glucose production • Improve insulin sensitivity	Metformin	Glucophage, Glucophage XR, Fortamet, Glumetza Riomet	• Dolutegravir increases metformin concentrations
Sulfonylureas	• Stimulate insulin release from the pancreatic β cells • Reduce glucose output from the liver • Increase insulin sensitivity	Glimepiride Glyburide Micronized glyburide Glipizide	Amaryl Diabeta, Micronase Glynase Glucotrol, Glucotrol xl	
Thiazolidinediones	• Lower blood glucose by improving target cell response to insulin • Do not increase pancreatic insulin secretion	Rosiglitazone Pioglitazone	Avandia Actos	• When used with CYP2C8 inhibitors (many PIs), rosiglitazone/pioglitazone levels may increase. Monitor carefully.
Incretins				
GLP-1 Analogues	• Increase glucose-dependent insulin secretion • Decrease inappropriate glucagon secretion • Increase β-cell growth/replication • Slow gastric emptying	Liraglutide Exenatide Exenatide LAR	Victoza Byetta Byetta LAR	
DPP-IV inhibitors	• Increase insulin synthesis and release from pancreatic β cells • Decrease glucagon secretion from pancreatic α cells • Decreased glucagon secretion results in decreased hepatic glucose production	Sitagliptin Saxagliptin Vildagliptin Linagliptin	Januvia Onglyza Galvus Tradjenta	• Gliptins have molecular targets on immune cells; however, no evidence that gliptin use changes CD4 or HIV RNA • Saxagliptin interacts with strong CYP3A4/5 inhibitors (eg, ritonavir); reduce saxagliptin dose when used with CYP3A4/5 inhibitors
Gliflozins	• Reduce reabsorption of filtered glucose from the tubular lumen and lower the renal threshold for glucose • Increase urinary excretion of glucose	Dapagliflozin Canagliflozin	Farxiga Invokana	• If UGT enzyme inducers (eg, ritonavir) are coadministered with canagliflozin, consider increasing the dose to 300 mg
Meglitinides	• Stimulate insulin release from pancreatic β-cells	Repaglinide Nateglinide	Prandin Starlix	• When used with CYP3A4/CYP2C8 inhibitors (many PIs), Repaglinide/nateglinide levels may increase. Monitor carefully. • EFV and ETR may increase nateglinide

Abbreviations: CYP, cytochrome P450; DPP-IV, dipeptidyl peptidase 4; EFV, efavirenz; ETR, etravirine; GLP-1, glucagon-like peptide 1; HIV, human immunodeficiency virus; LAR, long-acting release; PI, protease inhibitor; UGT, UDP-glucuronosyltransferase.

Insulin

Insulin is the preferred second-line medication for patients with HbA1c ≥8.5%. The major advantage of insulin is that it can produce major (ie, unlimited) reductions in HbA1c. However, insulin can cause hypoglycemia, it is associated with weight gain, and the insulin analogues (eg, glargine or detemir insulin) are costly. Recently, concern was raised for mitogenic effects of long-acting insulin due to binding with the insulin-like growth factor 1 receptor. However, several large studies showed no effect of long-acting insulin on cancer incidence [51].

Starting Insulin

Insulin therapy can be initiated with bedtime insulin glargine, insulin detemir, or insulin Neutral Protamine Hagedorn at a dose of 10–15 units, with a dose increase of 2–3 units every 3 days until the fasting glucose is <120 mg/dL (6.7 mmol/L) [52]. Adding prandial short-acting insulin (now available in both injected and inhaled forms) [53] may be beneficial if the fasting glucose goal is not achieved with long-acting insulin alone. Insulin is recommended as first-line therapy for patients with HbA1c >9%, severe liver disease, or severe kidney disease [34].

Incretins

Glucagon-like peptide 1 (GLP-1) regulates glucose homeostasis by decreasing β-cell workload and improving β-cell response. After eating, GLP-1 is secreted into the circulation by the L cells (neuroendocrine cells) of the distal ileum and colon. In the β cells, GLP-1 enhances glucose-dependent insulin secretion. GLP-1 also regulates gastric emptying, decreasing insulin demand, decreases postprandial glucagon secretion, and increases satiety [54]. There are two available therapeutic classes that influence GLP-1: GLP-1 analogues and dipeptidyl peptidase 4 (DPP-IV) inhibitors. GLP-1 analogues have the same effects as endogenous GLP-1 but a longer half-life, and DPP-IV inhibitors block the DPP-IV enzyme, which breaks down GLP-1.

Currently available GLP-1 analogues include exenatide, liraglutide, and exenatide long-acting release. The advantages to GLP-1 analogues are a 1% decrease in HbA1c, no hypoglycemia, weight loss, and preservation of β-cell mass/function. Their disadvantages include gastrointestinal side effects (primarily nausea) and high cost. Postmarketing trials are under way to examine possible increased pancreatitis, thyroid cancer, and pancreatic cancer risk [55]. Currently available DPP-IV inhibitors include sitagliptin, saxagliptin, vildagliptin, and linagliptin. Their advantages are similar to those of GLP-1 analogues. Disadvantages include a relatively small reduction in HbA1c (0.5%), gastrointestinal side effects (decreased intensity compared with GLP-1 analogues), possible hypersensitivity reaction, and high cost. Although a possible CVD risk reduction benefit with gliptins was reported, the benefit was not shown in subsequent studies, with one study reporting an increased rate of hospitalization for heart failure [56–58]. Concern regarding gliptin use in HIV-infected individuals was raised, as gliptins have molecular targets on immune cells; however, a small study revealed no changes in CD4 or HIV RNA among treated HIV-infected patients taking sitagliptin [59]. Of note, saxagliptin interacts with strong cytochrome P450 3A4/5 inhibitors (eg, ritonavir), and saxagliptin dose should be reduced when used in combination [60].

Considering the different second-line options, many clinicians would choose a sulfonylurea due to the high efficacy at low cost with a long track record of safety and efficacy. A large National Institute of Diabetes and Digestive and Kidney Diseases–funded trial comparing the sulfonylureas, the incretins (both a DPP-IV inhibitor and a GLP-1 agonist), and long-acting insulin is under way [61]. Currently, decisions regarding second-line (and subsequent) therapy should be individualized, incorporating patients' clinical characteristics and preferences.

ADDITIONAL AGENTS

Gliflozins

Glucose is freely filtered in glomeruli, then reabsorbed in the proximal tubule by the sodium glucose co-transporter 2 (SGLT2). SGLT2 inhibitors such as dapagliflozin and canagliflozin block the reabsorption of glucose in an insulin-dependent fashion, and glucose is then excreted in the urine. The advantages of gliflozins include weight loss (approximately 2 kg), lower blood pressure (BP), and no hypoglycemia. The disadvantages include consequences of glycosuria (urinary tract infection and genital fungal infections), and potentially increased cardiovascular risk, particularly within the first 30 days of initiating canagliflozin [62]. Data from postmarketing studies further exploring this risk are still pending. No interactions between ART and dapagliflozin are expected; however, if UDP-glucuronosyltransferase enzyme inducers (eg, ritonavir) must be coadministered with canagliflozin, clinicians could consider increasing the dose to 300 mg [63].

Meglitinides

This class of medications includes repaglinide (Prandin) and nateglinide (Starlix), which are short-acting medications that increase insulin release. They are dosed immediately prior to a meal, and offer the advantages of less hypoglycemia than the sulfonylureas and more flexibility with dosing. However, they are expensive, require frequent dosing, and only have a modest effect on HbA1c. For these reasons, they are not frequently used.

GLYCEMIC TARGETS

The standard glycemic target for patients with DM is HbA1c <7%, representing a mean blood glucose <150 mg/dL (8.3 mmol/L), fasting and preprandial values <130 mg/dL (7.2 mmol/L), and postprandial glucose <180 mg/dL (10 mmol/L) [34]. In monitoring DM therapy, HIV clinicians should consider that the HbA1c goal may need to be more stringent in HIV-infected patients, reflecting the underestimation of glycemia by HbA1c in HIV. Achieving glycemic targets, particularly in the setting of aggressive therapy in newly diagnosed diabetes [64], may decrease macrovascular complications of DM (coronary artery disease, cerebrovascular disease, and peripheral vascular disease), although study results have been mixed [65–67].

Achieving glycemic targets has been shown to decrease microvascular (retinopathy, neuropathy, and nephropathy) complications of DM [64, 66, 67]. However, adverse consequences of more intensive glucose control have been observed in clinical trials, including increased severe hypoglycemia and increased death [68, 69]. This underscores the need for individualization of targets. For example, patients with low HbA1c at baseline (ie, mild DM) tended to do better with more intensive targets for DM control. Furthermore, tighter control (HbA1c 6.0%–6.5%) is more appropriate for younger, healthier patients, whereas looser control (HbA1c 7.5%–8.0%) may be more

Table 3. Drug Interactions Between Statins and Antiretroviral Therapy

Statin	Interactions
Atorvastatin	PI
	Significant ↑ in atorvastatin levels with most PIs.
	TPV/r: contraindicated.
	For other PIs, Start with lowest dosage (10 mg). Monitor antilipid activity and titrate the statin dosage cautiously.
	NNRTI
	EFV: ↓ in atorvastatin levels; may need ↑ dosage.
	ETR: ↓ in atorvastatin levels; may need ↑ dosage.
	RPV: no dosage adjustments.
	Integrase inhibitor
	EVG/cobicistat/TDF/FTC: ↑ atorvastatin possible. Start with lowest dosage. Monitor response and titrate dosage cautiously.
Fluvastatin	PI
	Not well studied; no known significant interactions with most PIs.
	NNRTI
	ETR: may ↑ fluvastatin. Monitor response and titrate dosage cautiously.
Lovastatin	PI
	Substantial ↑ in statin levels, high risk of adverse effects.
	Contraindicated.
	NNRTI
	ETR, NVP: ↓ lovastatin possible. Monitor response.
	Integrase inhibitor
	EVG/cobicistat/TDF/FTC: significant ↑ lovastatin expected; contraindicated.
Pitavastatin	PI
	No dosage adjustments necessary.
	NNRTI
	EFV: No dosage adjustments necessary.
Pravastatin	PI
	Variable effects; moderate ↑ pravastatin AUC and C_{max} with most. No dosage adjustment of pravastatin is required.
	Exceptions:
	DRV/r: Consider alternative statin. If prescribed, use lowest possible dosage, monitor carefully.
	SQV + RTV: ↓ pravastatin AUC. May need to ↑ pravastatin dosage to reach lipid goals.
	NNRTI
	EFV: ↓ pravastatin AUC May need to ↑ pravastatin dosage to reach lipid goals.
Rosuvastatin	PI
	ATV/r: ↑ rosuvastatin C_{max}. Consider alternative statin. If prescribed, use lowest possible dosage (5 mg/day), monitor carefully. Do not exceed 10 mg/day.
	DRV/r: ↑ rosuvastatin C_{max}. Use lowest possible dosage, monitor carefully.
	LPV/r: ↑ rosuvastatin C_{max}. Consider alternative statin. If prescribed, use lowest possible dosage, monitor carefully. Do not exceed 10 mg/day.
	TPV/r: ↑ rosuvastatin C_{max}. Use lowest possible dosage, monitor carefully.
	Integrase inhibitor
	EVG/cobicistat/TDF/FTC: rosuvastatin AUC ↑ 38%, C_{max} ↑ 89%; titrate statin dose accordingly.
Simvastatin	PI
	Substantial ↑ in simvastatin levels, high risk of adverse effects.
	Contraindicated.
	NNRTI
	EFV: ↓ simvastatin AUC >50%. May need to ↑ simvastatin dosage to reach lipid goals.
	ETR, NVP: ↓ simvastatin possible.
	Integrase inhibitor
	EVG/cobicistat/TDF/FTC: Significant ↑ simvastatin expected; contraindicated.

Adapted from Department of Health and Human Services Guidelines for the use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents (Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf Tables 18a, 18b, and 18d) and Primary Care of Veterans With HIV Manual (section on lipid-lowering medications-ARV interactions); see http://www.hiv.va.gov/provider/manual-primary-care/lipid-lowering-meds.asp).

Abbreviations: ↓, decrease; ↑, increase; ARV, antiretroviral; ATV/r, ritonavir-boosted atazanavir; AUC, area under the curve; C_{max}, maximum serum concentration; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir; TDF, tenofovir; TPV/r, ritonavir-boosted tipranavir.

appropriate for older patients with multiple comorbidities who are prone to hypoglycemia [34].

MACROVASCULAR ENDPOINT PREVENTION—ADDITIONAL CONSIDERATIONS

CVD risk factors (dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of albuminuria) should be assessed annually. Routine noninvasive CVD screening in asymptomatic patients, with the exception of annual pedal pulse assessment, is not recommended. Peripheral arterial disease screening includes annual assessment of pedal pulses and consideration of ankle-brachial index testing. Screening for cerebrovascular disease is not recommended [25].

Comprehensive CVD Risk Reduction

HIV-infected patients have higher risk of CVD compared with HIV-uninfected controls [6, 70], likely caused a combination of factors including metabolic derangement, lifestyle factors such as smoking, and chronic inflammation. Patients with both HIV and DM are at particularly high risk. Comprehensive interventions have been shown to have a significant impact on CVD among patients with DM [71] and should include:

A: Antiplatelet therapy
B: Blood pressure management
C: Cholesterol management
D: Diabetes/glucose management
S: Smoking cessation

Antiplatelet Therapy

Patients with increased CVD risk should receive aspirin (ASA), although ASA resistance, or "lower than normal antiplatelet response to standard doses of aspirin," is common, reported in up to 57% of general population patients taking aspirin [72], sometimes making ASA ineffective. A pilot study of ASA in HIV-infected patients showed that heightened platelet activation and immune activation in treated HIV disease was attenuated by 1 week of ASA therapy. This is a potential additional benefit of ASA in patients with HIV and DM [73].

Blood Pressure

The Joint National Committee (JNC) 8 guidelines recommend that patients with DM aged ≥18 years start pharmacologic therapy to lower BP at systolic blood pressure (SBP) >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg to treat to goals SBP <140 mm Hg and DBP < 90 mm Hg [74]. JNC 8 guidelines recommend that black patients with DM include a thiazide diuretic or calcium channel blocker (CCB) in their antihypertensive regimen and that nonblack diabetic patients include a thiazide diuretic, CCB, angiotensin-converting enzyme inhibitor (ACE), or angiotensin receptor blocker (ARB) in their regimen.

Cholesterol Management

The ACC/AHA cholesterol treatment guidelines recommend that all patients with DM aged 40–75 years with low-density lipoprotein cholesterol (LDL-c) 70–189 mg/dL without clinical atherosclerotic cardiovascular disease take a moderate-intensity (if calculated 10-year CVD risk is <7.5%) or high-intensity (if 10-year calculated CVD risk is ≥7.5%) statin [75]. These guidelines recommended checking therapeutic response 4–12 weeks after starting therapy and every 3–12 months thereafter. The expected LDL-c reduction is at least 50% with a high-intensity statin and 30%–50% with a medium-intensity statin.

Clinicians should engage in individualized discussions with their patients, taking into consideration that less aggressive treatment and/or targets may be appropriate for certain patients. Multiple drug interactions between statin therapy and antiretroviral therapy exist (Table 3), requiring careful selection and monitoring of therapy [37].

MICROVASCULAR ENDPOINT PREVENTION—ADDITIONAL CONSIDERATIONS

To help prevent microvascular complications, patients should have yearly ophthalmologic exams to detect retinopathy. To avoid nephropathy, good BP and lipid control are crucial, along with a spot urine microalbumin every 12 months to screen for nephropathy as well as ACE inhibitor or ARB treatment in patients with DM with hypertension or microalbuminuria. Patients should have foot exams every 6–12 months and instruction in foot care, with a referral to podiatry if there is evidence of neuropathy (Table 4) [25].

CONCLUSIONS

DM is a prevalent chronic condition with many deleterious effects, which may be accentuated among patients with both DM

Table 4. Prevention of Microvascular Complications in Patients With Diabetes Mellitus

Target Area	Recommendation
Retinopathy	Yearly ophthalmologic exam
Nephropathy	Optimize blood pressure and lipid control
	Spot urine microalbumin every 6 mo to screen for nephropathy
	ACE inhibitor/ARB in patients with hypertension or microalbuminuria
Neuropathy	Foot exams every 6–12 mo
	Instruction in foot care
	Referral to podiatry if evidence of neuropathy

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

and HIV. We recommend that clinicians perform regular DM screening in HIV-infected patients; however, we do not recommend using HbA1c for screening. In treating DM, lifestyle changes are critical, as a 5%–10% weight loss can have important metabolic effects. If drug treatment is required, metformin is first-line therapy. Decisions regarding second- and third-line drugs should be individualized. The HbA1c goal is <7% in most patients, but should be individualized depending on a patient's other comorbidities. A comprehensive approach to prevent micro- and macrovascular complications among HIV-infected patients with DM will lead to the best outcomes.

Note

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