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How sweet it is?

Susceptibility to diabetes mellitus in HIV-I treatment

Treatment of HIV-I infection with combined antiretroviral therapy substantially improves survival and quality of life, but is associated with metabolic disturbances such as insulin resistance, dyslipidemia and body fat partitioning disorders. These metabolic complications in the setting of suppression of viral replication are associated with increased observed risk for Type 2 diabetes mellitus. Disorders of glucose metabolism present additional challenges in the management of HIV infection, including the long-term complications of hyperglycemia, such as nephropathy, neuropathy and retinopathy, and magnified cardiovascular risk. This article considers how HIV infection and its treatment increases susceptibility to disorders of glucose metabolism. Diagnostic criteria, historical and clinical antecedents that assist the clinician in detection of diabetes susceptibility and treatment objectives are discussed.

KEYWORDS: adipokines ■ diabetes ■ diabetes mellitus ■ HIV ■ insulin resistance ■ insulin secretion ■ lipodystrophy ■ metabolic syndrome ■ obesity ■ visceral obesity

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Learning objectives

Upon completion of this activity, participants should be able to:

- Identify risk factors for diabetes associated with HIV infection
- Specify medications used to treat HIV that are associated with a higher risk for incident diabetes
- Diagnose diabetes effectively among patients with HIV infection
- Treat diabetes according to current recommendations

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HIV infection affects an estimated 33 million people globally [101]. Based on data available from nations contributing to UNAIDS, the Joint United Nations Program on HIV/AIDS and WHO surveys, there were 2.7 million new cases of infection and 2 million deaths in 2007 [101]. Two thirds of people living with HIV infection live in sub-Saharan Africa; infection rates appear to be declining in some countries, but are increasing in others including Indonesia, Vietnam, the Russian Federation and Ukraine, in addition to more affluent nations in western Europe [101]. Concurrently, there is a worldwide epidemic of diabetes mellitus, mostly attributable to the global increase in overweight people and obesity. The International Diabetes Federation (IDF) estimates 246 million adults have diabetes mellitus, affecting 6% of adults in nations contributing to IDF surveys [102]. The global prevalence of diabetes mellitus has increased fivefold over almost two decades [102]. As the prevalence of obesity increases, it is extrapolated this will increase global diabetes mellitus prevalence by 50% over the next two decades [1].

The diagnostic criteria for diabetes mellitus and its precedents are listed in **Table 1** [2]. The most common form of diabetes, Type 2 diabetes mellitus (T2D), most frequently occurs in the setting of genetic susceptibility associated with the environmental factors of overweight or obesity, increasing caloric intake and sedentariness. The most common form of diabetes occurring in HIV infection is T2D. Hyperglycemia appears to evolve through several phases that can be detected prior to the onset of T2D, including impaired fasting glucose and impaired glucose tolerance. Insulin deficiency (absolute or relative) is critical to the development of hyperglycemia. Insulin resistance is a major factor promoting the development of pancreatic β -cell secretory impairment and T2D.

This article summarizes the current knowledge regarding prevalence and pathogenesis of disorders of glucose metabolism in HIV infection, in addition to clinical treatment objectives.

Glucose disorders in treated HIV infection & potential susceptibility factors

■ HIV infection

HIV infection *per se* appears to have little effect on glucose metabolism. Prior to effective antiretroviral therapy, diabetes mellitus was infrequent; rates of diabetes mellitus were

estimated at less than 3% [3,4]. HIV seropositivity did not appear to have any effect on fasting glucose in cross-sectional studies of untreated HIV-infected and control subjects [5]. Early treatment-associated cases of diabetes mellitus were associated with the use of the pancreatic β -cell toxic pentamidine, in the setting of pneumonia [6], where it induced hyperglycemia analogous to Type 1 diabetes mellitus with ketoacidosis and the requirement for insulin therapy [6].

In HIV-infected subjects receiving antiretroviral therapy, fasting glucose concentrations were higher than in untreated HIV-infected subjects, despite similar abdominal obesity [5]. Data from this large study suggested HIV therapy increased the relative risk (RR) of diabetes 2.2-fold [5].

Where combined antiretroviral therapy (cART) is available, the clinical management of HIV infection has markedly improved. Early cases of T2D in the cART era were linked to initiation of protease inhibitor (PI) therapy, appearing within the first year of PI initiation [7–9]. Multiple metabolic complications to cART were also apparent, including hypercholesterolemia, hypertriglyceridemia, lipodystrophy and lipohypertrophy.

■ Disorders of body fat: obesity & lipodystrophy

Obesity, particularly abdominal obesity, appears to be the strongest physical factor promoting T2D in the general population. Other body fat disorders are also associated with T2D, such as congenital and acquired lipodystrophy; HIV-associated lipodystrophy is now the most common form of lipodystrophy and may directly promote hyperglycemia.

Prospective observational studies of HIV-associated lipodystrophy provided the first strong evidence of an increased risk for glucose disorders in treated HIV infection. In a study of HIV-associated lipodystrophy, baseline T2D prevalence was 2% [10] and increased over threefold after 14 months [11], which suggests lipodystrophy strongly promotes the progression to hyperglycemia. The overall prevalence of all glucose disorders (T2D, impaired fasting glucose and impaired glucose tolerance) was 25% [11]. In the Lipodystrophy Case Definition Study ($n = 1081$ cART recipients), diabetes prevalence was 7% in those with lipodystrophy and 3% in those without [12]. Other studies have also reported higher rates of glucose disorders in cART-associated lipodystrophy:

Table 1. Criteria for diagnosis of diabetes mellitus and glucose disorders (American Diabetes Association cutoffs).

	Diabetes mellitus	Impaired glucose tolerance	Impaired fasting glucose
Fasting glucose*	>7.0 mmol/l >126 mg/dl	–	5.6–6.9 mmol/l 100–125 mg/dl
2-h glucose†	>11.1 mmol/l >200 mg/dl	7.8–11.0 mmol/l 140–200 mg/dl	–
Random glucose	>11.1 mmol/l >200 mg/dl with symptoms‡	–	–

*Fasting is defined as no caloric intake for at least 8 h.
†Following a 75 g anhydrous glucose load dissolved in water.
‡Including polyuria, polydipsia and unexplained weight loss.
Data taken from [4].

rates of T2D and impaired glucose tolerance were 7 and 35%, respectively, versus 0.5 and 5%, respectively, in healthy, seronegative controls [13]. It should be noted, however, that these studies analyzed specific cART components of that time, which have changed in modern regimens in use in affluent nations. Certain PIs such as ritonavir and indinavir (which potently increase insulin resistance) and nucleoside analogs such as stavudine (implicated in lipoatrophy) [14–17] are less frequently used in modern drug regimens in affluent nations. This therapy shift may alter reported prevalence of glucose disorders in HIV-infected patients no longer or never exposed to these drugs; however, as these drugs are frequently used in resource-poor settings we can expect to continue to see their dysglycemic effects.

Obesity prevalence rates appear similar in HIV-infected persons to that of the general population, at least in the USA. A large study of over 1600 HIV-infected subjects reported overweight and obesity prevalence rates of 31 and 14%, respectively [18]. Obesity promotes insulin resistance and the progression of β -cell failure. It is thus possible that HIV-infected patients with coexisting obesity may have a higher prevalence of diabetes than that reported prior to the obesity epidemic. There are no conclusive data yet. However, data from the Veterans Aging Cohort Study from the USA supports this suggestion [19]. T2D prevalence was compared in over 3200 HIV-infected veterans to similar numbers of non-HIV-infected persons. T2D prevalence was 15% in HIV-infected subjects, compared with 21% in noninfected subjects, who were older and had a threefold higher prevalence of obesity [19]. No comparisons were made in BMI-matched controls to remove the expected effect of obesity.

■ cART drug components in incidence studies

Two large prospective studies provide important information on incidence rates and specific drugs that may promote T2D susceptibility. The Multicenter AIDS Cohort Study of approximately 1000 HIV-infected subjects reported T2D incidence rates of 10% of cART recipients over 4 years, compared with 3% in HIV-seronegative men [5]. After adjustment for age and BMI, this represented a greater than fourfold increase in the RR for T2D [5]. PI use was associated with an odds ratio risk of 1.06 [5]. Ritonavir use was associated with the highest RR for developing T2D (RR: 1.70) in statistical models that controlled for age, BMI, CD4⁺ cell count, and cumulative use of nucleoside reverse-transcriptase inhibitors (NRTIs) and non-NRTIs [5].

A further prospective study, The Data Collection on Adverse Events of Anti-HIV Drugs, recently reported T2D incidence in over 33,000 treatment-naïve patients at 5.7 cases per 1000 person-years [20]. Age, BMI and longer duration of infection were significant predictors [20]. Stavudine exposure was associated with the highest risk for incident T2D (RR: 1.19), with increased risk also evident for zidovudine (RR: 1.06) and didanosine (RR: 1.06), but a lower risk for ritonavir (RR: 0.94) and nevirapine (RR: 0.89) [18].

The Women's Interagency HIV Study of over 1500 HIV-infected women estimated T2D incidence on cART to be 3.4 per 100 person-years [21]. After adjustment for confounders, longer cumulative exposure to NRTIs was associated with higher risk for T2D: for 0–3 years of exposure the RR was 1.81 and for more than 3 years of exposure the RR was 2.64 [21]. Cumulative PI and non-NRTI exposure did not predict incident T2D after adjustment for confounders [21]. The

findings of these studies suggest there may be differences in drug susceptibility between men and women.

■ Genetic & ethnicity-associated susceptibility

Type 2 diabetes mellitus in HIV infection can also be expected to vary from one population to another, and is modified by factors such as genetic susceptibility. Family history of T2D has been found to be a risk for developing T2D in HIV-infected patients receiving PIs [22]. In this case-control study, an odds ratio of 3.3 was found for family history of T2D, in age-, gender- and ethnicity-matched controls [22]. A Taiwanese study recently found that family history was the strongest predictor of incident T2D (RR: 2.66), as discussed later [23]. By contrast, two studies have found no increased susceptibility in subjects with a family history of T2D [11,24].

Ethnicity-associated susceptibility to the development of T2D is suggested in several studies. A prospective study from the Los Angeles area found a T2D prevalence of 12% amongst all PI recipients at baseline; 77% of the cohort were African-Americans and 17% were Latinos [25]. After 3 years, T2D incidence was 7%, all cases were African-Americans [25].

Most T2D prevalence and incidence data in HIV infection are from western nations. Insights on ethnic susceptibility are offered from the Swiss HIV Cohort Study, which found African or Asian ethnicity to be associated with a T2D RR of 2.2 and 4.9, respectively [26]. It is worth noting that this cohort would have been treated with regimens in use in affluent nations.

Informative, early data are emerging from Africa and Asia, where HIV infection may be treated later with older, relatively inexpensive regimens. A recent prospective study from Benin reported 2-year metabolic complications after initiation of first-line cART [27]. Within the relatively short time frame of this study and (relative to western nations) an absence of obesity-promoting environmental accelerators, T2D developed in 8% of subjects, with lipohypertrophy in 24%, lipoatrophy in 9%, hypercholesterolaemia in 35% and metabolic syndrome in 13% [27]. Prospective observational data from Taiwan indicate an incidence of 13 T2D cases per 1000 person-years, with an average of 4.6 years follow-up [23]. Screening was by fasting glucose alone; risks for incident diabetes mellitus were family history, hypertriglyceridemia, current PI use and past exposure to zidovudine [23]. These early data

suggest sub-Saharan and Asian populations may be at heightened risk of metabolic complications including T2D; further studies are awaited.

■ Gender

Data on the prevalence of glucose disorders in HIV-infected women are few. A 12% prevalence of T2D in HIV-infected female cART recipients, compared with 13% in HIV-negative women, using the 75 g oral glucose tolerance test has been reported, suggesting no significant increase in incidence using the most sensitive screening tool [28]. However, a significant confounder in this study was the disparity in obesity prevalence between the two groups: 86% of HIV-negative women were overweight or obese versus 67% in HIV-infected subjects; abdominal obesity was significantly lower in the HIV-infected groups [28]. Both of these anthropometric factors may have lessened overall risk of T2D in the HIV-infected women.

Data from the Women's Interagency HIV Study found the incidence of T2D to be 2.8% in HIV-infected women receiving PIs and 1.2% in HIV-infected cART-naïve women, similar to HIV-negative controls [29]. Obesity rates in the HIV-negative control women were significantly higher; however, T2D incidence rates in controls were half that in treated HIV-infected women [29]. These data suggest that female cART recipients may develop T2D at lower adiposity levels. Data are emerging on diabetes mellitus during pregnancy. In the Pediatric AIDS Clinical Trials Group, gestational diabetes was found to occur more frequently in PI recipients [30]. By contrast, another study reported gestational glucose intolerance was not associated with PI use [31]. Rates have been estimated at 8% [32,33], with maternal age [31,33], Hispanic ethnicity [31], and PI or stavudine exposure [33] identified as risks.

■ Hepatitis C

Coexistent HCV infection with HIV infection appears to increase diabetes risk in some [19,34], but not all studies [26]. HCV infection is associated with higher insulin resistance [35]. In a retrospective study of over 1200 HIV-infected cART recipients (50% co-infected with HCV), the prevalence of T2D doubled in HCV co-infection, 5.9% compared with 3.3% [34]. T2D incidence was higher in those with HCV co-infection: 5.8% compared with 2.8% [34]. By contrast, in the Swiss HIV Cohort Study of over 6500 subjects, HCV co-infection did not appear to increase risk of incident T2D [26]. Similarly,

data from the Veteran's Aging Cohort Study did not find HCV co-infection in HIV-infected subjects to increase T2D risk [19].

■ Metabolic syndrome

Metabolic syndrome, a clustering of clinical and biochemical phenotypes including central obesity, hypertension and dyslipidaemia, is considered a precedent of T2D. Several classifications exist; diagnostic criteria for the two classifications most frequently used in clinical studies [36,37] are presented in **Box 1**.

The debate surrounding the predictive value of metabolic syndrome pivots around whether, as a composite, it predicts a multiplicative or additive increase in risk for T2D and cardiovascular disease.

Data suggest that the presence or development of metabolic syndrome increases T2D risk in treated HIV infection. Early descriptions of HIV-associated lipodystrophy recognized the presence of metabolic syndrome phenotypes [10]. Several studies have reported criteria-defined metabolic syndrome in treated HIV-infected patients. A Spanish study of over 700 subjects using National Cholesterol Education Program ATP-III criteria reported a prevalence rate of 17%; identified risks were BMI and PI exposure (past or present) [38]. PI use was the strongest risk for metabolic syndrome with an odds ratio of 4.2; after age- and BMI- adjustment, metabolic syndrome was related to stavudine (odds ratio: 1.74) and lopinavir/ritonavir use (odds ratio: 2.46) [38]. The US Nutrition in Healthy Living Study reported the prevalence of metabolic syndrome at 24% in over 400 subjects; metabolic syndrome was associated with higher viral load, BMI and use of lopinavir/ritonavir or didanosine [39]. The incidence of metabolic syndrome was 1.2/100 person-months, predicted by increasing viral load, weight and lopinavir/ritonavir or didanosine use [39]. Potential confounders included high rates of obesity (over 50%) and lower socioeconomic status [39]. Another study, the HIV Lipodystrophy Case Definition Study of over 700 subjects, found metabolic syndrome prevalence rates of 14–17% [24]. Prevalence rates of T2D were 5–9-times higher in those with metabolic syndrome, compared with those without [24]. By contrast, a study of over 400 HIV-infected subjects from the USA reported metabolic syndrome prevalence at 25%, which they found to be similar to National Health and Nutrition Examination Survey (NHANES) prevalence for a HIV-negative cohort [40].

Box 1. International Diabetes Federation and National Cholesterol Education Program-ATP III criteria for metabolic syndrome.

International Diabetes Federation [37]

- Waist >94 cm men/>80 cm women
- Plus two of:
 - Glucose >5.6 mmol/l
 - High-density lipoprotein <1.20 mmol/l
 - Triglycerides >1.7 mmol/l
 - Systolic blood pressure >130 mmHg
 - Diastolic blood pressure >85 mmHg

National Cholesterol Education Program-ATP III [38]

- Any three of:
 - Waist >102 cm men/>88 cm women
 - Glucose >6.1 mmol/l
 - High-density lipoprotein <1.0 mmol/l in men/<1.2 mmol/l in women
 - Triglycerides >1.7 mmol/l
 - Blood pressure >130/85 mmHg

Metabolic syndrome development after cART initiation in treatment-naïve HIV-infected subjects is described in at least two studies. Metabolic syndrome prevalence increased from a pretreatment rate of 16 to 25% after 48 weeks of cART; metabolic syndrome incidence was 14 per 100 patient-years [41]. In a 3-year prospective study, metabolic syndrome incidence was 12 per 100 patient-years after cART initiation [42]. The presence of metabolic syndrome at cART initiation increased the risk for incident T2D fourfold; risk for incident T2D in those developing metabolic syndrome was increased four- to fivefold (42) [42].

Unique factors that may influence development of metabolic syndrome require discussion; these include: trends in obesity, nutrition, physical activity, genetic and ethnic susceptibility, stress, maternal nutrition, birthweight and other factors. Changes in drug exposures may also influence metabolic syndrome prevalence in the future. Metabolic syndrome is discussed in detail elsewhere [43].

■ Insulin resistance

Insulin resistance underlies T2D and is considered a core precedent. Insulin resistance is not altered in untreated HIV infection, shown by early studies using the gold standard measure of insulin sensitivity, the hyperinsulinemic, euglycaemic clamp [44]. Single drug studies in HIV-negative subjects found indinavir reduced insulin sensitivity by 30% using clamp [45]. In a separate study of HIV-negative subjects, ritonavir reduced insulin sensitivity by 15%; no effect was found with amprenavir [46]. In treatment-naïve HIV-infected subjects, insulin sensitivity by clamp reduced 3 months after initiation of ritonavir-boosted

lopinavir plus zidovudine/lamivudine [47]. By contrast, ritonavir-boosted lopinavir plus nevirapine had no observable effect on insulin sensitivity [47].

In vivo clinical studies and *in vitro* cell model studies have helped determine the mechanisms of antiretroviral therapy-induced insulin resistance. All PIs acutely reduced insulin-stimulated glucose uptake in adipocytes [48]. Cell culture studies found that PIs reduce GLUT4 translocation independently of insulin signaling pathways [49]. Reduced phosphorylation of the key postreceptor insulin signaling pathway signaling molecule MAPK has also been demonstrated [50].

In addition to these cellular events, PIs also reduce adipocyte differentiation, influencing potent adipogenic proteins, such as sterol regulatory element-binding protein-1 and peroxisome proliferator-activated receptor- γ [50]. The regulation of insulin sensitivity and glucose metabolism is dependent on normal adipocyte differentiation, function and adipokine secretion of adipokines. PI effects on adipocyte function may thus play an indirect role in insulin resistance and glucose regulation.

As expected, lipodystrophy in HIV infection is also associated with insulin resistance [10,11,51], as lipodystrophy is a known insulin-resistant state. Studies using clamp methodology show a 50% lower insulin sensitivity in subjects with treated HIV and lipodystrophy, compared with age-, BMI- and waist-matched treated HIV controls never exposed to PIs [51].

Nucleoside reverse-transcriptase inhibitors have also been shown to induce insulin resistance in clamp studies [47]. After 4 weeks of stavudine treatment in healthy, HIV-negative controls, clamp insulin sensitivity was reduced, and associated with falls in striated muscle mitochondrial DNA and reduced mitochondrial function (by ^{31}P magnetic resonance spectroscopy) [52]. Stavudine-induced reductions in mitochondrial gene expression in adipose tissue were observed in HIV-negative controls [53]. Data published to date on cART-induced insulin resistance indicate independent class effects and possibly multiple intraclass effects for cART components, influencing different elements involved in the regulation of insulin resistance.

■ Inflammation

Increasingly, inflammation is implicated in the regulation of glucose metabolism; obesity-induced disturbances in circulating, low-grade inflammation are considered to accelerate the pathogenesis of T2D. Several studies have reported higher

circulating inflammatory molecules in treated HIV infection, including increased C-reactive protein, TNF- α , IL-6 and low adiponectin, in the context of suppressed viral replication [54–59]. Lipodystrophy is associated with an even greater proinflammatory profile, which is more exaggerated than that found in insulin-resistant obesity [59]. Circulating TNF- α levels and low adiponectin predicted insulin resistance measured by clamp, independent of body fat [59]. Metabolic syndrome in treated HIV infection is also characterized by higher C-reactive protein levels and lower adiponectin levels [24]. There are few data implicating drug class or exposures.

Case ascertainment & screening

Prevalence and incidence data on T2D in HIV infection are confounded by measurement. Some studies reported here relied on only fasting or random glucose for diagnosis, leading to under-detection. In Caucasian HIV-infected men, fasting glucose has been shown to be relatively insensitive for detecting T2D, with 72% of cases positive by the 75 g oral glucose tolerance test showing a nondiabetic fasting glucose [10,11]. These data suggest the 75 g oral glucose tolerance test should be standard for detection of diabetes mellitus, at least in this population and where resources permit.

Hb_{A1c} is the standard used to monitor long-term glucose control. Several recent studies have highlighted a possible discordance between Hb_{A1c} and glucose levels in treated HIV infection, suggesting Hb_{A1c} may under-represent overall glycemia [60,61]. Evidence of low-grade hemolysis (higher mean corpuscular volume and serum haptoglobin) in HIV-infected patients with diabetes mellitus was found to predict those patients whose Hb_{A1c} was lower than expected for glucose levels [60]. Nucleoside analogs in particular were associated with low-grade hemolysis [60]. These emerging data suggest caution in interpreting Hb_{A1c} in treated HIV infection, particularly in patients receiving nucleoside analogs, when use of fructosamine may be indicated.

Treatment targets in diabetes

The American Diabetes Association has issued treatment targets in diabetes mellitus, which cover not only glucose control, but risk factors identified to magnify diabetic complications and diabetic cardiovascular disease [62]. Achieving these targets relies upon patient education, empowerment and participation, with long-term objectives of sustained lifestyle change involving improved nutrition and increased physical

activity, achieving and maintaining optimal weight, and, where necessary, appropriate medications for glycemia, blood pressure and lipid control and complication management. Essential components of care involve physical examination to detect neuropathy, hypertension, retinopathy and laboratory investigations to ensure adequate control of blood glucose, lipids and to detect nephropathy (summarized in **Table 2**) [62].

Notwithstanding the studies cited here, few data are available on diabetes treatment trends and complication rates in treated HIV infection. A recent survey conducted at a Chicago center with a large cohort of uninsured HIV-infected patients found 54% of patients with diabetes mellitus met the American Diabetes Association target of an Hb_{A1c} level of less than 7% [63], slightly above what data indicate were national averages in the USA in 2004 [64]. There was evidence of lipid checks in the majority of patients; 70% had received nutritional consultation, 62% urinalysis and 18% foot examination [63]. No data are presented for retinal examination. A total of 56% of patients were on target for blood pressure targets, with similar numbers reaching lipid targets [63]. Of interest, patients with diabetes receiving PIs had triglyceride levels that were 50% higher than those not [63]. Suppressed viral load was associated with lower frequency of meeting lipid targets [63],

consistent with the well-recognized lipid-raising effects of combined antiretroviral therapy. In those patients who underwent urinalysis, a high rate of proteinuria was apparent (50%) [63], suggesting selection bias, increased susceptibility to diabetes-associated proteinuria or multifactorial causes. Of interest, HIV-infected women with diabetes achieved treatment targets less frequently; the authors suggest this may represent the perception of lower cardiovascular risk, as evidenced by lower rates of aspirin use [63]. The authors suggest useful strategies for managing HIV-infected patients with diabetes mellitus within primary care settings where there are competing management issues. These include flagging patients with diabetes mellitus and providing checklists detailing required clinical examination, lipid and microalbuminuria screening. Group patient education on nutrition, glucose monitoring and foot care are suggested, as are annual primary care physician updates from endocrinologists [63].

Conclusion

Available data suggest that patients with treated HIV infection have increased susceptibility to T2D. In part, this appears to be due to drug-specific effects, lipodystrophy, metabolic syndrome, ethnicity and co-infection with hepatitis C. Changes in the global demographics of

Table 2. Recommendations for standard of care in diabetes mellitus.

	Clinical examination	Laboratory	Multidisciplinary
Initial evaluation	Weight status		Diabetes education Diet and exercise prescription
	Blood pressure		
	Lipids	Fasting lipids	
	Macrovascular complications		
	Microvascular complications: retinal, neuropathy and nephropathy	Spot urinary albumin/creatinine ratio	Ophthalmic and podiatry review
Treatment targets	Smoking status		Smoking cessation
	Weight		Individualized management plan for healthy weight
	Glycemia	$Hb_{A1c} < 7.0\%$, performed at least biannually	Lifestyle and medications
	Blood pressure: sBP <130 mmHg dBP <80 mmHg	Performed every routine visit	Lifestyle and medications
	Lipids: LDL <100 mg/dl (<2.6 mmol/l) Antiplatelet agents	Performed annually, at least	Diet, statin or fibrate (statin if overt CVD) Aspirin
Annual review	Lipids	Spot urinary albumin/creatinine ratio	
	Retinal examination		
	Foot examination for pulses and neuropathy		

CVD: Cardiovascular disease; dBP: Diastolic blood pressure; LDL: Low-density lipoprotein; sBP: Systolic blood pressure.
Adapted from [62].

HIV infection will also have an impact, with higher infection rates present in populations with genetic susceptibility to diabetes mellitus in countries with rapidly changing lifestyle and obesity rates. Further studies are required, across different populations in particular, to document the longer term complications of hyperglycemia in HIV infection.

Future perspective

The prevention, early detection and management of diabetes mellitus presents clinical challenges that will expand into almost every area of medicine, promoted by the epidemic of obesity. In 'at-risk' individuals, such as the HIV-infected patient receiving antiretroviral therapy, the above factors will force themselves into everyday care.

The challenges for clinicians involved in treating patients with HIV infection will include the best drug regimen for virological control but with minimalized individual risk for metabolic and cardiovascular complications. Aggressive risk-factor management for Type 2 diabetes and its associated cardiac risk will include an appropriate eating and physical activity regimen, control of weight, cessation of smoking and other substance abuse and, where necessary, drug therapy. Little data are available on the relative efficacy of these approaches in treated HIV infection, compared with the noninfected population. Over the next 5–10 years, it is anticipated that these data will emerge, as will data demonstrating whether patients with treated HIV infection and T2D are at higher risk of the complications of diabetes.

Executive summary

- Diabetes mellitus affects 6% of the adult world population; however, prevalence rates are rapidly increasing owing to obesity and lifestyle changes. A fivefold increase in prevalence is predicted over the next 20 years.
- Treated HIV infection is associated with at least a doubling of risk for diabetes mellitus.
- Risk factors include exposure to older antiretroviral therapies (e.g., zidovudine, zalcitabine and didanosine), abdominal obesity, lipodystrophy, co-infection with hepatitis C and presence of metabolic syndrome.
- Diabetes mellitus develops when insulin secretion cannot meet insulin demands, owing to insulin resistance, obesity, infection and other factors.
- Insulin resistance is induced by different antiretroviral drugs, including some protease inhibitors, nucleoside reverse transcriptase inhibitors and non-nucleosides. However, not all drugs within each of these classes induce insulin resistance.
- A fasting glucose exceeding 7.0 mmol/l or a 2-h glucose (after a 75 g oral glucose load) of more than 11.0 mmol/l is diagnostic of diabetes mellitus.
- Lifestyle intervention with modest weight loss and increased physical activity in people at risk of diabetes will reduce progression to hyperglycemia.
- Suboptimal glucose control in diabetes mellitus causes renal failure, neuropathy, blindness and cardiovascular disease. Diabetes treatment focuses on optimal glucose control and aggressive cardiovascular risk factor management.

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
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1. Which of the following statements about risk factors for diabetes among patients infected with HIV is most accurate?

- ☐ A HIV infection itself promotes impaired fasting glucose
- ☐ B Lipodystrophy among patients with HIV may directly promote hyperglycemia
- ☐ C Obesity is three-times as common among patients with HIV compared with the general population
- ☐ D Coexistent hepatitis C infection reduces the risk for diabetes associated with HIV infection

2. Which of the following medications used to treat HIV infection is least likely to promote incident diabetes?

- ☐ A Efavirenz
- ☐ B Stavudine
- ☐ C Indinavir
- ☐ D Ritonavir

Activity continued overleaf...

3. According to the current review, what is the preferred way to test patients with HIV for the presence of diabetes?

- ☐ A Fasting glucose
- ☐ B Random glucose
- ☐ C 75 g oral glucose tolerance test
- ☐ D Glycated hemoglobin A1c level

4. Which of the following outcomes fits into the treatment goals espoused by the American Diabetes Association?

- ☐ A Hemoglobin A1c level less than 6.5%
- ☐ B Systolic blood pressure less than 140 mmHg
- ☐ C Diastolic blood pressure less than 90 mmHg
- ☐ D Low-density lipoprotein cholesterol level less than 100 mg/dl