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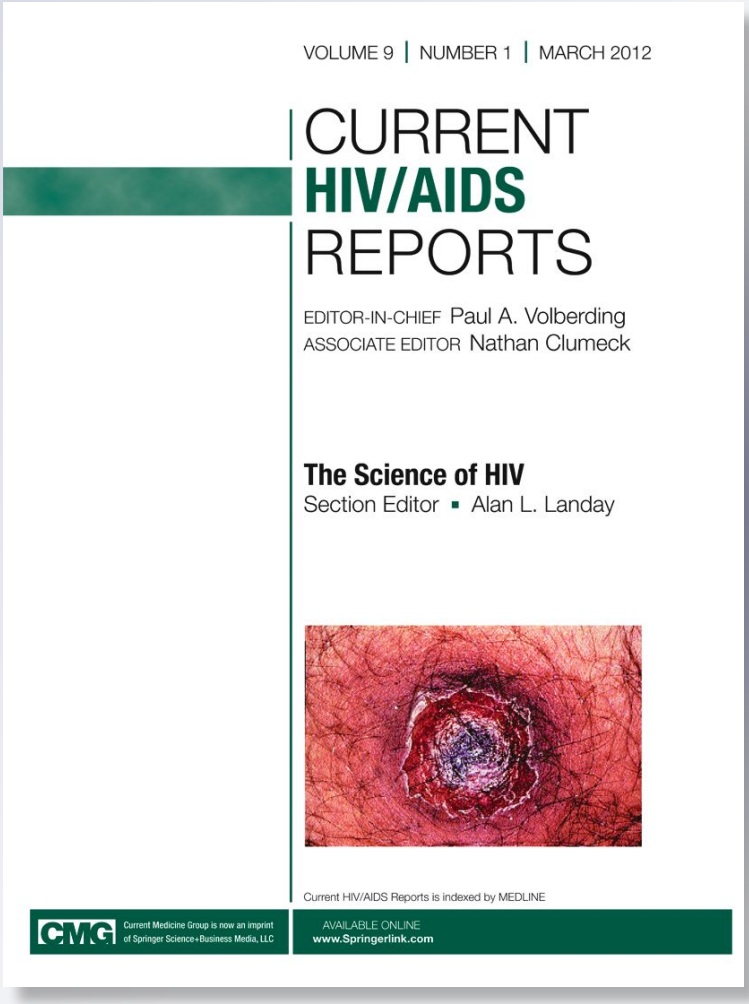

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METABOLIC COMPLICATIONS AND COMORBIDITY (JM KILBY, SECTION EDITOR)

The Burden of Diabetes and Hyperlipidemia in Treated HIV Infection and Approaches for Cardiometabolic Care

Katherine Samaras

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Abstract Treatment of HIV infection with highly active antiretroviral therapy (HAART) confers survival and quality of life benefits. However, these significant benefits are at the cost of metabolic complications with associated increased risk of type 2 diabetes and cardiovascular disease. These chronic diseases add complexity to the standards of care in HIV infection and much remains unknown about the natural histories of diabetes and hyperlipidemia in this setting. This review examines recent research findings in diabetes and hyperlipidemia in HIV infection, juxtaposed on our prior understanding of these diseases. It also reviews the current evidence base and clinical guidelines for diabetes and lipid management and cardiometabolic prevention in HIV-infected HAART recipients.

Keywords Diabetes · HIV · Insulin resistance · Lipid · Fat · Myocardial infarction · Heart · Metabolic · Hyperlipidemia · Cardiometabolic care

Introduction

HIV infection affects 39.5 million people worldwide [1]. HIV- and AIDS-related morbidity and mortality have reduced significantly since the availability of highly active antiretroviral therapy (HAART). The priorities of HIV care are focused primarily on suppression of viral replication and immune system restoration. However, the cardiometabolic sequelae of HIV treatment, in addition to the aging of the HIV-infected population, have extended the complexity of care to management of comorbidities such as diabetes and cardiovascular disease (CVD).

This review describes very recent advances in the understanding of diabetes and hyperlipidemia in HIV infection and their treatment. Literature over the past 10 years has described the increased risk of people with treated HIV infection to diabetes and CVD. It is appropriate that HIV physicians develop expertise in identification and treatment of diabetes and CVD risk factors and that preventive and early intervention measures are instituted.

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Diabetes Mellitus

Definition

Diabetes mellitus (diabetes) is the state of hyperglycemia that develops when pancreatic β-cell insulin secretion is insufficient to meet insulin needs, the latter determined by individual levels of insulin resistance and intake of carbohydrate-containing foods. Diabetes is defined as a fasting glucose>126 mg/dL (7.0 mmol/L), a plasma glucose level exceeding 200 mg/dL (11.1 mmol/L) 2 h after a 75-g oral glucose load, or two random plasma glucose levels exceeding 200 mg/dL (11.1 mmol/L with symptoms of hyperglycemia [thirst, polyuria, polydipsia, or recurrent infections]) [2]. Diabetes is preceded by a prodrome of perhaps 5 years or more, with β-cell dysfunction evident with an impaired fasting glucose (100–125 mg/dL [5.6–6.9 mmol/L]), or impaired glucose tolerance (plasma glucose>140–199 mg/dL [7.8–11.0 mmol/L]) 2 h after a 75-g oral glucose load).

Diabetes affects about 336 million people [3]. Distinct ethnic susceptibilities are evident, particularly where there have been rapid transitions from traditional lifestyles to

affluent lifestyles characterized by sedentariness and consumption of high energy-density foods. About 7 million people develop diabetes each year; diabetes is expected to affect 438 million people by 2030 [3].

Diabetes Prevalence and Incidence in HIV Infection

Prior to the introduction of HAART, disorders of glucose metabolism were uncommon in HIV infection, with early studies suggesting diabetes rates of 2.0–2.6 % in treatment-naïve HIV-infected subjects [4, 5]. Since the advent of HAART, a number of cases have been reported indicating rapid onset of diabetes after protease inhibitor initiation [6–8], and these may be due to unique susceptibility. Early studies show varied rates of diabetes and need to be considered within the context of that era: early protease inhibitors and nucleoside reverse transcriptase inhibitors, and the presence of lipodystrophy and obesity and ethnic predisposition within study cohorts. For example, diabetes affected 2 % in one HAART-associated lipodystrophy cohort [9], rising to 7 % after 14 months observation with a 25 % prevalence of all glucose disorders [10]. These rates are comparable to contemporaneous studies [11]. A recent cross-sectional study reports diabetes and impaired fasting glucose prevalence rates of 4.5 % and 9.1 %, respectively [12]. Longer-term studies have shown a fourfold increase in relative risk of incident diabetes: in 10 % of HAART recipients over 4 years, compared to 3 % in HIV-seronegative controls [13].

Diabetes incidence data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) followed 33,389 HIV-infected subjects over an average of 3.8 years [14]. Case ascertainment was by fasting glucose or physician report of antidiabetic therapy initiation. Diabetes prevalence at baseline was 2.9 % and incidence was 5.72 cases/1000 patient-years follow-up [14].

The Swiss HIV Cohort Study reported diabetes prevalence at baseline at 4 % in 8444 participants, with a stepwise increase in prevalence based on age (2.1 %<50 years, 7.0 % in 50–64 years, and 16.2 % in > 65 years) [15••]. Over a 3-year follow-up period, the prevalence rose to 7 %, with an estimated incidence of 3.12 cases/1000 patient-years follow-up [15••].

While the Swiss Cohort and D:A:D studies are similar for sex distribution (70–73 % male) and HIV transmission (43 % men who have sex with men, 30–40 % heterosexual transmission, 17–18 % intravenous drug use), there are notable cohort differences including median HIV infection duration (5 years in D:A:D, 15 years in the Swiss Cohort) and the frequency of HAART-naïve participants (27.1 % and 6.5 %, respectively) [14, 15••].

Other important recent studies include a 10-year study of 1046 participants, representing 7846 person-years follow-up [16••]. Diabetes ascertainment was by glucose levels or commencement of antidiabetic medication. Diabetes incidence was 14.1 cases/1000 patient-years follow-up [16••]. A further study is one of few including participants "at-risk of HIV infection"; the study of 377 participants found baseline rates of diabetes of 7 % and prediabetes of 31 % [17], and incident cases of diabetes (5 % over a median of 18 months) were not associated with HIV seropositivity or HAART [17].

Risk Factors Predisposing to Diabetes

Standard Diabetes Risk Factors

Age

Age is a consistent predisposing risk factor for incident diabetes [14, 15••, 16••]. The Swiss HIV Cohort reported age-stratified incidence rates quadrupling over a difference of 15 or more years. Incidence in participants<50 years: 2.09/1000 patient-years follow-up; 50–64 years: 4.65/1000 patient-years follow-up; and > 65 years: 8.56/1000 patient-years follow-up [15••]. Similarly, the recent French 10-year study found a 3.6-fold increased incidence for participants > 50 years [16••]. The effect of aging on diabetes prevalence is well documented in HIV-negative populations.

Sex

Sex differences may be an important susceptibility consideration. Most published diabetes studies contain predominantly male participants. D:A:D reported that male sex was associated with a 60 % higher diabetes relative risk [14]. Data in women are relatively scant; however, a number of informative studies exist.

A study of 226 women with, or at risk of, HIV infection reported diabetes prevalence at 12 % in HIV-infected women HAART recipients and 13 % in HIV-uninfected participants [18]. Obesity was much more prevalent in HIV-uninfected participants; nevertheless, diabetes rates were higher than expected given the age range (35–70 years) [18].

The Women's Interagency HIV Study has reported a diabetes incidence of 2.8 % over 3 years in protease inhibitor recipients, versus 1.2 % in HAART-naïve and 1.4 % in the HIV-uninfected participants [19]. HIV-uninfected women were more frequently overweight or obese (33 % vs 23 % in the HIV-infected women), yet had half the rate of incident diabetes [19], indicative that female HAART recipients are at greater diabetes susceptibility at lower adiposity. More recently, the Women's Interagency HIV Study reported diabetes incidence was dependent on drug exposure: the rate of incident diabetes was 1.6 and 1.9 times higher in HIV-

infected women receiving protease inhibitors or a non-protease inhibitor regimen, compared to HIV-infected women with no recent HAART [20].

Thus, while HIV-infected women receiving HAART appear to have a lower risk of developing diabetes compared to men, diabetes develops with lesser adiposity and exposure to different drug regimens. The latter may reflect sex differences in drug metabolism and elimination, particularly since women more frequently have reduced hepatic drug elimination.

Family History

An interesting question is whether HIV infection and HAART accelerate the age-related β-cell dysfunction observed in the general population, magnify underlying (genetic) diabetes susceptibility, or act directly on diabetes pathogenesis. Older age may represent a longer duration of HIV infection, but this is often included as a covariate. Age may also reflect exposure to older agents and a higher risk of lipodystrophy. Family history (a surrogate for genetic susceptibility) has been associated with incident diabetes in some [21], but not all studies [10, 16••, 22].

Obesity and Visceral Obesity

An important consideration in diabetes risk evaluation in HAART is the impact of weight gain and obesity. Without argument, obesity is the major environmental factor accelerating progression to diabetes in the susceptible, evidenced in countries that have undergone rapid lifestyle transitions with rapidly rising rates of obesity, where HIV infection rates are also significant (eg India and Thailand). Obesity increases insulin resistance and progression of the β-cell secretory defect. Thus, weight gain and obesity in HAART recipients may magnify any diabetes risk inherent in HIV treatment.

Obesity increases risk of incident diabetes in HIV. In D:A:D, diabetes rates were twofold and more than fourfold higher in overweight (26–30 kg/m^2) and obese participants (>30 kg/m^2), compared to healthy body mass index [14]. Similarly, the hazard ratio of incident diabetes was reported at 1.91 for overweight and 2.85 for obese participants in a 10-year incidence study [16••]. Fat distribution is more predictive than body mass index for incident diabetes: a higher sex-appropriate waist-hip ratio was associated with a 3.87-fold increased risk of incident diabetes [16••].

Lipid Disturbances and Metabolic Syndrome

Diabetes dyslipidemia is characterized by elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, is associated with prediabetes, and is independently associated with incident diabetes. Its presence is a hallmark of insulin resistance, visceral obesity, and the metabolic derangements that are strongly associated with diabetes.

The D:A:D Study Group found higher triglyceride levels and low HDL were independently predictive of incident diabetes [14]. Twofold higher triglyceride levels were associated with an 80 % increased risk of incident diabetes [14]. Conversely, high HDL was protective: a 1-mmol/L higher HDL halved incident diabetes risk [14]. Higher total cholesterol was also predictive [14]. Thus, lipid disturbances reflect systemic metabolic disturbances and are a simple, cheap screening tool that can assist in early identification of those at risk of diabetes development.

Metabolic syndrome describes the cluster of central obesity, dyslipidemia, and elevated blood pressure and glucose. It is a risk predictor for diabetes.

Diabetes prevalence is five- to ninefold higher in HIV-infected people with metabolic syndrome [22]. In the prospective observational INITIO Study, metabolic syndrome at HAART initiation was associated with a 4.34-fold increased risk of incident diabetes; interestingly, incident metabolic syndrome on HAART was associated with a slightly higher risk of incident diabetes (hazard ratio of 4.89) [23]. These data suggest that rapid changes in metabolic parameters after HAART initiation either confer additional diabetes risk, or perhaps induce diabetes in susceptible individuals.

Hepatitis C co-infection

Hepatitis C infection is associated with increased insulin resistance [24]. The impact of co-existent hepatitis C and HIV infection on diabetes risk is controversial. A retrospective study of HIV-infected HAART recipients, 50 % co-infected with hepatitis C virus, found diabetes prevalence rates in co-infected participants were twice that of HIV infection alone (5.9 % vs 3.3 %); incident diabetes at 4.9/100 person-years in co-infected participants versus 2.3 in HIV infection alone [25]. In contrast, a recently published 10-year prospective study found hepatitis C co-infection did not confer additional risk [16••]. Era-specific differences in the HAART regimens may explain these divergent results; nevertheless, it is not unreasonable to still consider hepatitis C infection as a future risk factor for diabetes, as it is in the HIV-uninfected.

HIV-Specific Diabetes Risk Factors

In addition to the standard risk factors for diabetes being perhaps more prevalent, it is necessary to consider HIV-specific factors that have been associated with increased risk.

Duration Infection and CD4 Counts

Recent studies of incident diabetes have found no association with known duration of HIV infection or nadir CD4 count [14, 16••].

Drug Exposures

While the virus itself may not be implicated in diabetes pathogenesis, initiation of antiretroviral therapy is, operating through a number of pathways. The first is a regain of weight and well-being that occurs after HAART initiation; this return to health is associated with weight gain, improved appetite, and caloric intake. The second is the effect of specific antiretroviral drugs on aspects of glucose metabolism, by increasing insulin resistance or impairing insulin secretion, thus promoting hyperglycemia.

Exposure to specific antiretrovirals is also related to risk of diabetes. The potential of a medication to induce disturbances in glucose metabolism is best evaluated in short-duration studies in HIV-negative volunteers, with a few informative studies. For example, single doses of ritonavir at 800 mg [26] or lopinavir (533 mg) with ritonavir 133 mg [27] acutely deteriorated insulin sensitivity, whereas amprenavir 1200 mg did not [26]. Two recent studies contribute further to our understanding as to why diabetes risk is increased in HAART recipients. A single 200-mg dose of ritonavir (such as is used to boost other protease inhibitors) in seronegative volunteers did not deteriorate insulin resistance, suggesting that some drug effects are dose-dependent [28]. In a further study, lopinavir 400 mg with ritonavir 100 mg administered to seronegative volunteers for 4 weeks did not alter insulin secretion or insulin resistance [29], supporting dose-dependent adverse effects on glucose metabolism, but also that other factors may be involved in diabetogenesis. Further, this study showed deteriorated lipid profile with increased triglycerides and HDL [29]. Clearly longer-term studies with these medications cannot be conducted in seronegative volunteers; however, it is possible these disturbances may have adverse metabolic effects in the long term.

Observational studies in HIV-infected cohorts indicate associations with individual drugs, but also exposure effects. Duration of exposure to antiretroviral therapy is a consistent factor associated with increased incident diabetes risk. In D:A:D, cumulative HAART exposure was independently associated with incident diabetes, increasing the relative risk of diabetes by 11 % [14]. Overall, no consistent picture has emerged for drug class susceptibility. Stavudine exposure in D:A:D had the strongest relationship with incident diabetes (19 % increase in relative risk), though exposure to zidovudine and didanosine also carried increased risk; ritonavir and nevirapine exposure appeared protective [14].

A recent 10-year incidence study stratified drug exposure and duration [16••]. Exposure to indinavir for <12 months was associated with an incident diabetes hazard ratio of 2.56; exposure to stavudine for <1 year or 1–2 years was associated with similar hazard ratios: 2.56 and 2.65 [16••]. Didanosine exposure for 2–3 years was associated with a threefold risk of incident diabetes [16••].

Body Fat Partitioning Disorders

The impact of body fat partitioning disorders on diabetes prevalence also requires consideration. Lipodystrophy presence appears to accelerate failure of insulin secretion, with early observational studies showing a sevenfold rise in diabetes prevalence in the relative short term [10]. In the Lipodystrophy Case Definition Study, where half the cohort had lipodystrophy, diabetes prevalence was twofold higher in those with lipodystrophy (7 % vs 3 %) [30]. As stavudine exposure was strongly linked to lipoatrophy [31–33], alterations in HAART regimens have diminished lipodystrophy prevalence, at least in affluent nations. Recent studies of incident diabetes indicate presence or progression of lipodystrophy is associated with higher incident diabetes risk, with hazard ratios of 1.28 [14] and 2.14 [16••]. Differences in risk might be attributed to cohort differences, drug exposures, and duration of observation. Nevertheless, the presence of lipodystrophy should identify individuals at diabetes risk, who may benefit from diabetes prevention strategies. Readers are referred to comprehensive reviews of lipodystrophy and its treatment [34, 35], and the pathogenesis of diabetes in HIV infection [36, 37].

Considerations in Resource-Poor Settings

Evidence for diabetes risk in resource-poor settings is evolving. Specific considerations are differences in obesity, diet, and, importantly, reliance on older drugs that are now infrequently used in affluent nations. Further, rapid lifestyle changes in some countries have resulted in rising obesity and diabetes rates overall, particularly evident in Southern and Southeast Asia.

Mathematical modelling has attempted to consider the impact of HAART on projected diabetes incidence. Using assumptions based on data from other incidence studies, the wider availability of HAART within South Africa has been estimated to increase diabetes incidence from 1 % to 11 % [38]. A Johannesburg study of relatively young HIV-infected participants (18–45 years) receiving HAART for > 1 year, found <1 % diabetes prevalence, though lipid disturbances were present in half [39].

A systematic review on diabetes from Sub-Sahara African cohorts found diabetes prevalence varied from 1 to 12 %, with 5-year mortality ranging between 4 and 57 % [40]. In considering these very surprisingly high mortality rates, it is important to note that type 1 diabetes (representing ~10 % of all cases) requires insulin replacement as an absolute necessity. Insulin can be difficult or impossible to access in resource-poor settings for reasons of cost and administrative and delivery difficulties. Even though less expensive, standard diabetes medications and care are also

costly. In resource-poor settings where HAART options are limited to drug regimens associated with higher diabetes risk, are we setting HIV-infected people up for virological control at the expense of other diseases where access to care and medications will be limited?

Diabetes increases infection risk and reduces immunity particularly when poorly controlled, a critical consideration in countries with high rates of tuberculosis infection. Data indicate high prevalence rates of both diabetes and HIV infection in tuberculosis cohorts in south India, 32 % and 9 %, respectively [41]. Data are needed on the combined impact of diabetes and HIV infection on the outcomes of common infectious diseases such as tuberculosis.

Diabetes Complications in HIV Infection

Despite the adverse metabolic milieu of HAART and diabetes, data on diabetes complications in HIV infection and its treatment are scant. Are the hyperlipidemia [42], inflammation [43, 44], or medications used to treat HIV infection associated with acceleration or severity of diabetes micro- and macrovascular complications? Recent publications in the literature suggest the affirmative, particularly for nephropathy.

Low-level albuminuria is an early marker of diabetic nephropathy. Annual urine screening for albumin presence is a standard in routine diabetes care. A recent study reported that HIV-infected participants with diabetes have rates of albuminuria twice that in HIV-uninfected controls (34 % vs 13 %) [45]. Albuminuria was related to viral load and cumulative exposure to abacavir [45]. A retrospective analysis of > 22,000 HIV-infected participants in the Veteran's Affairs (VA) register found the presence of diabetes independently increased risk of end-stage renal disease by 70 %, as did hypertension, CVD, but also HIV-related factors such as viral load, CD4 count, and hepatitis C co-infection [46].

There is also early evidence supporting lower cu-offs for diabetes risk indices in HIV infection. For example, urine albumin levels within the normal range predicted an eight-fold higher rate of microalbuminuria and a fourfold increased rate of renal dysfunction by 2 years [47]. Diabetes independently predicted a fourfold increased rate of microalbuminuria [47]. More data are required specifically in cohorts with HIV infection and diabetes.

Little data exist for retinopathy in diabetes in HIV-infected cohorts. One sub-Sahara African study of diabetic retinopathy prevalence found that sight-threatening diabetic retinopathy was not associated with HIV infection [48]. More data are required in this area, as for neuropathy. Neuropathy is relatively common in HIV infection, often related to HAART toxicity. Little is known as to whether diabetes alters the natural history of HAART-related neuropathy, or whether HIV infection per se is associated with higher rates of diabetic neuropathy.

There is growing evidence that diabetes is associated with accelerated cognitive decline [49•]. A recent report indicates the presence of diabetes in HIV infection is also associated with neurocognitive impairment in older participants [50•].

Data on the impact of diabetes on macrovascular disease in HAART recipients are emerging. Diabetes was independently associated with a 2.4-fold higher rate of incident coronary heart disease in the D:A:D study, less than those with pre-existing heart disease (7.5-fold higher risk) [51].

Diabetes Standards of Care and Guidelines

The American Diabetes Association's Standards of Care in Diabetes details annually appropriate care of people with diabetes and is an excellent evidence-based resource to guide specialized and general medical practitioners and allied health professionals [52]. Readers are referred to this excellent resource that documents appropriate screening, treatment, education, and self-care [52].

At a minimum, people with diabetes require annual assessment and screening for complications, including retinal and foot examination and urinary albumin screening. It is appropriate to examine patients at 3–6 monthly intervals to ensure glycemic, lipid, and blood pressure targets are met.

Antidiabetic treatment in people with HIV infection requires consideration of adverse events susceptibility, summarized in Table 1.

There is evidence that people with HIV infection are undertreated for cardiovascular risk factors. A recent German HIV cohort study found 56 % of people with diabetes received antidiabetic treatment and 41 % with known coronary heart disease received antiplatelet agents [53]. Using national and international risk criteria, 30 % of participants at high risk of coronary heart disease plus elevated low-density lipoprotein (LDL) cholesterol were untreated; similarly, 50 % at moderate risk of coronary heart disease plus elevated LDL cholesterol did not receive treatment [53]. This study highlights undertreatment of known cardiometabolic risk factors in HIV infection in an affluent nation where treatment barriers are not expected. Reasons for undertreatment require identification and intervention, as they are likely to contribute to poorer long-term health.

There is also emerging evidence of lesser diabetes control in HIV-infected people. The VA diabetes/HIV cohort

Table 1 Drug interactions and considerations between HAART and antidiabetic and lipid-lowering medications

	HAART class or drug	Effects / interactions
Antidiabetic medications		
Metformin	Stavudine	Risk of lactic acidosis
	Tenofovir	Risk of lactic acidosis
Insulin secretagogues (all sulfonylureas, repaglinide)	All HAART	Safe
Dipeptidyl peptidase (IV) inhibitors (sitagliptin, vildagliptin, saxagliptin)	All HAART	No data yet
		Theoretical risk of immunodeficiency and infection
Insulin	All HAART	Safe
Lipid-lowering medications		
Simvastatin	Protease inhibitors	Extensive block of cytochrome P450 3A4 metabolism, substantial increases in simvastatin levels and risk of toxicity
Rosuvastatin	Lopinavir-ritonavir Darunavir-ritonavir (suspected)	Serum rosuvastatin levels increase fivefold
Atorvastatin	Lopinavir	Serum atorvastatin levels increase two- to sixfold
	Saquinavir-ritonavir	Lower doses required to treat
	Darunavir Fosamprenavir	A maximal dose of 20 mg is suggested if on protease inhibitors [1]
	Efavirenz	Serum atorvastatin levels reduce by 35 %, thus higher doses may be needed to reach therapeutic targets
Pravastatin	Lopinavir-ritonavir	Reduces pravastatin levels by 50 %, higher doses may be needed
	Darunavir-ritonavir	Increases pravastatin levels by 80 %; care with toxicity
	Nelfinavir	Reduces pravastatin levels by 45 %, higher doses may be needed
	Efavirenz	Reduces pravastatin levels by 40 %, higher doses may be needed
Fluvastatin	Protease inhibitors	Appears safe
Ezetimibe	Protease inhibitors	No interactions
Gemfibrozil	Protease inhibitors	No interactions
Fenofibrate	Protease inhibitors	No interactions
Bile acid binding resins	All HAART	May reduce absorption of HAART Avoid, unless using once-daily HAART, which is administered at least 4 h prior to once-daily bile acid binders
Fish oils	All HAART	Safe
Extended-release niacin	All HAART	Safe

HAART—highly active antiretroviral therapy

Adapted from Dubé and Cadden [42]

showed that while rates of glucose, lipid, and blood pressure control screening were high, they were less than in the general VA cohort [54]. Further, there were differences in centers with a low and high HIV caseload, with the authors concluding that "high performance can be achieved and is a reasonable expectation at all facilities" [54]. A second recent study compared diabetes treatment targets achieved in an academic urban setting to the American Diabetes Association's standards; inadequate glycemic control was evident in 33 %; suboptimal blood pressure control in 58 %; suboptimal LDL control in 34 %; and suboptimal triglycerides in 69 % [55]. Complication screening was also less frequently performed than recommendations: 53 % and 81 % of the cohort had not undergone screening for retinopathy and nephropathy, respectively, as is required [55].

Few HIV-specific diabetes care guidelines exist. A notable exception is a consensus document promulgated very recently from South Asia [56], which recognizes the paucity of data in people with HIV and diabetes [56].

Hyperlipidemia

Lipid disorders are highly prevalent in HIV-infected HAART recipients, occurring at HAART initiation. They contributing to higher cardiovascular risk, as do traditional lifestyle factors (smoking [57] and obesity [58]), but also HIV-specific factors including immune reactivation, viremia [59], inflammation [59], and specific antiretroviral drugs. It is not the intention of this review to comprehensively review HAART and lipid disorders; readers are referred to a recent review of this area [42]. A number of recent studies are relevant to lipids and excessive cardiovascular morbidity in HIV infection.

CVD Prevalence and Risk

CVD has become one of the major non-AIDS complications; as many as 9–20 % of HIV-infected people in developed countries have a moderate or high increase in 10-year risk of myocardial infarction [60, 61]. Rates of myocardial infarction in different studies vary between 0.35 and 11.1/100 person-years follow-up [62••, 63••, 64, 65••]. In considering CVD, it is noteworthy that traditional risk factors in HIV-infected people are high, reviewed elsewhere [57]. Smoking cessation, a standard first-line intervention in CVD risk reduction, was associated with a 40 % reduction in incident CVD in D:A:D by 12 months [66].

Exposure to different HAART medications and incident myocardial infarction has been evaluated in a number of studies, with conflicting data. Recently, the D:A:D Study Group reported an association between myocardial infarction and recent exposure to abacavir and didanosine, or cumulative exposure to indinavir and lopinavir-ritonavir [67]. The abacavir association remains controversial, with supportive [59] and negative papers [68, 69]. No associations have been found between myocardial infarction risk and use of tenofovir, zidovudine, stavudine, lamivudine, or zalcitabine, nor to cumulative exposure to nevirapine, efavirenz, nelfinavir, or saquinavir [67]. It is interesting that some of the observed risk was reduced by adjustment for lipids, suggesting at least some of the observed drug associations with myocardial infarction are mediated by drug-induced disturbances in lipid metabolism. Different lipid subfractions have been shown to be independently predictive of incident myocardial infarction or CVD, including cholesterol, triglyceride, small dense LDL, and apolipoprotein B levels [59, 62••, 70].

Interventions

Readers are referred to the excellent summary of management of lipid disorders in HIV infection, including the evidence for nonpharmacological and pharmacologic treatments [42].

The importance of early intervention for prevention of lipid disturbances has been highlighted very recently in the first randomized dietary study in HIV-infected participants. At initiation of HAART, participants were randomized to receive advice every 3 months from a dietitian for 12 months for dietary fat reduction and caloric control versus no advice [71]. At 12 months, participants receiving dietary advice were spared the rise in total and LDL cholesterol observed in controls and had lower triglycerides than at baseline, while triglycerides rose in controls; these differences were clinically significant [71]. The dietary intervention was associated with a two-thirds lower dyslipidemia rates by 12 months, compared to controls (21 % vs 68 %) [71]. An important secondary outcome was that the intervention blunted weight gain after HAART initiation, perhaps an important mediator of the metabolic disturbances observed with HAART. The long-term durability of dietary advice and the ongoing need for dietary advice is yet to be determined; however, these data indicate simple dietary advice is efficacious, at least in the short term.

Lipid-lowering treatment in people with HIV infection requires consideration of HAART interactions and adverse events susceptibility, summarized in Table 1. Lipid targets in HIV-infected people are the same as those applied to the general population; as yet, there is no evidence that lower targets are required.

HIV-infected people at high risk of myocardial infarction appear to receive less-than-standard care, as found with diabetes: only 36 % of D:A:D Study participants with prior myocardial infarction were receiving lipid-lowering therapy [67]. This apparent undertreatment requires further investigation to address the barriers to standard care, such that cardiometabolic care in those with HIV infection is equal to that of uninfected individuals.

Metabolic Screening and Risk Evaluation in the HIV-Infected Patient

"Healing is a matter of time, but it is sometimes also a matter of opportunity."

-Hippocrates

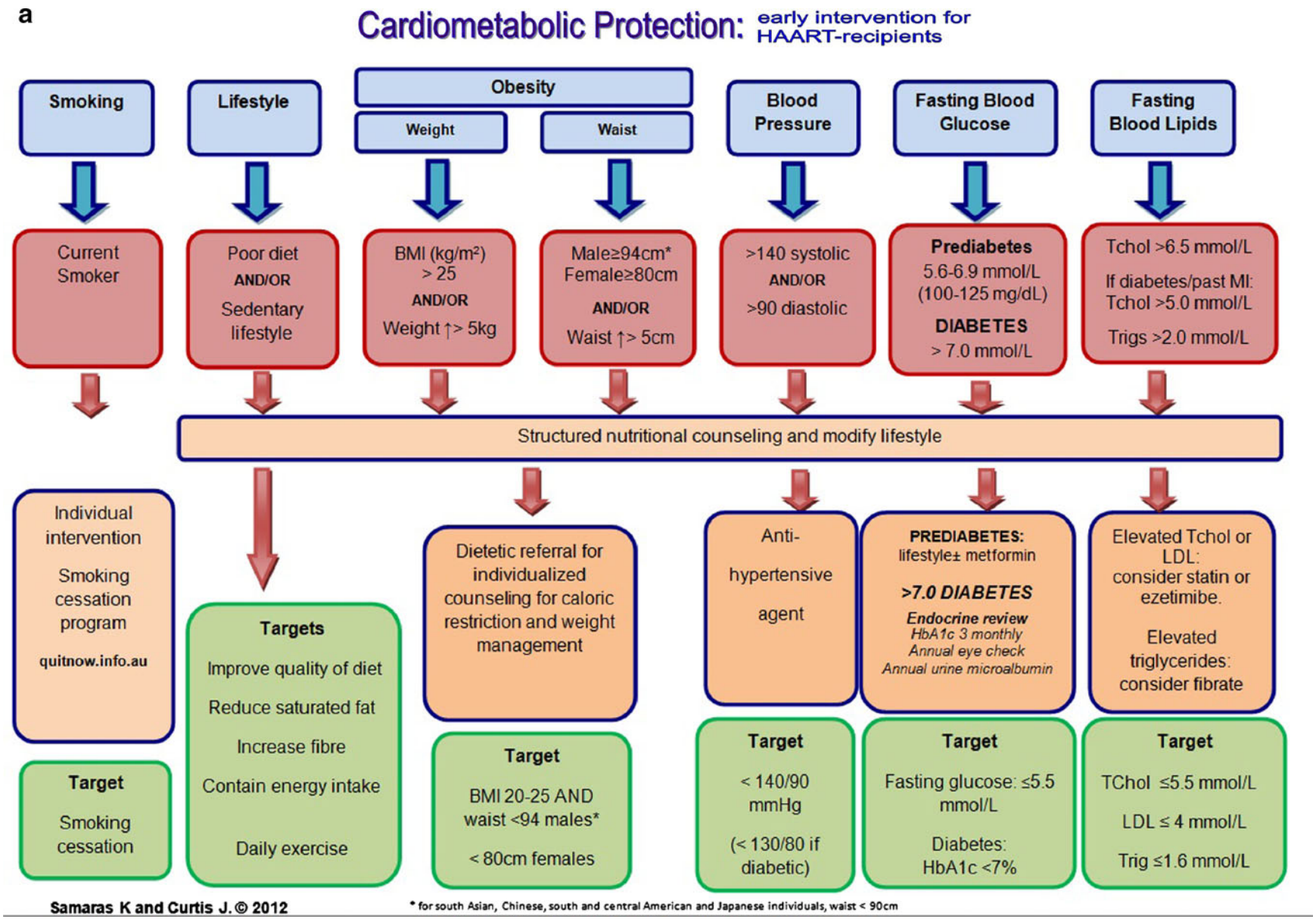

Fig. 1 **a** and **b**, HIV-specific clinical algorithm for cardiometabolic protection in youth with psychosis. BMI—body mass index; BP—blood pressure; CVD—cardiovascular disease; HAART—highly active antiretroviral therapy; HbA1c—hemoglobin A1c; HDL—high-density lipoprotein; LDL—low-density lipoprotein; PCOS—polycystic ovary syndrome; PI—protease inhibitor; TChol—total cholesterol; Trig—triglyceride

b

History: smoking, exercise, diet, family history (CVD, diabetes, obesity), gestational diabetes, ethnicity, polycystic ovary syndrome in women.

Then at 3-6 monthly

Examination: weight, BMI, waist circumference, BP

Investigations: Fasting blood glucose and lipids: total cholesterol (TChol); LDL, HDL, triglycerides (Trig);

Don't just

SCREEN

→

INTERVENE

for all patients in the

"red zone"

Pharmacological Interventions:

Lipid lowering therapy:

Cholesterol lowering: initiation doses after failure of lifestyle measures to achieve targets

atorvastatin 10mg nocte	PI drug interactions: 20 mg max dose
pravastatin 10mg nocte	drug interactions may need↑ or ↓ dose
rosuvastatin 10 mg nocte	drug interactions: lower dose
simvastatin 10 mg nocte	PI drug interactions: lower dose or avoid
ezetimibe 10mg nocte	no interactions

Fibrate therapy for triglyceride lowering:

gemfibrozil 600 mg bd
fenofibrate 145 mg mane

Consider metformin if:

- •diabetes or impaired fasting glucose or
- •PCOS with obesity

Metformin therapy: start at 500mg x ½ tablet after breakfast and dinner for two weeks then increase to 500mg bd. If side-effects of nausea, abdominal cramping, shift to after meal.
CAUTION: any renal impairment or concomitant tenofovir or stavudine therapy

Anti-hypertensive therapy:
Multiple agents are available.

Anti-platelet therapy:
In diabetes or pre-existing cardiovascular disease.

Interventions:

Nutritional counseling: reduce take away and junk food, reduce energy intake to prevent weight gain, stop soft drinks and juices, increase fibre intake

Aim for fat intake < 25% of energy intake.

Increase soluble fibre intake.

Physical activity: structured education-lifestyle intervention. Advise daily physical activity: eg 30 minutes of walking, or accruing 10,000 steps each day (pedometer).

Switching: Consider HAART composition at initiation, based on family history, lipids, diabetes risk, to lipid and diabetes neutral medications.

HAART considerations:

Diabetes and prediabetes:

avoid PIs;

care with stavudine, didanosine and zidovudine.

Pre-existing cardiovascular disease:
multiple statin-HAART interactions
avoid abacavir

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Fig. 1 (continued)

A number of evidence-based guidelines exist for cardiometabolic evaluation in the general population and can be applied in HIV. The Framingham model was found to be an acceptable predictor of incident myocardial infarction by the D:A:D Study Group with a close relationship between observed and model-predicted events [61]. More recently, there is evidence that adding HIV-specific factors (exposure to indinavir, lopinavir-ritonavir, and abacavir) to a model of traditional CVD risks outperformed Framingham in predicting CVD events [72].

Given the increased risk for both diabetes and CVD in HAART recipients, it is reasonable and desirable that management of the HIV-infected individual includes not only cardiometabolic screening, but active intervention to prevent the common diseases. A philosophical view is to consider the merit of "cardiometabolic protection" in all HIV-infected HAART recipients, with cardiometabolic screening and early intervention with lifestyle management from initiation of HAART.

It is also reasonable to share established clinical resources used to screen and prevent in other high-risk clinical settings, such as schizophrenia, where the condition and the drugs used to treat it are associated with a 20-year shortening of life expectancy and high rates of premature cardiac disease and diabetes. Figure 1 is an HIV-specific adaptation of a clinical algorithm developed with collaborators (J. Curtis) for cardiometabolic protection in youth with psychosis [73]. The amended algorithm is offered for use in HAART recipients in nonspecialized settings and by general medical and allied health professionals; it requires not only screening at defined intervals, but indicates action points for intervention and internationally accepted treatment targets.

Conclusions

The enduring benefits of HAART have altered the natural history of HIV infection. These profound benefits are at the cost of metabolic complications that manifest with high risks for diabetes, lipid disorders, and premature CVD. Once virologic control is established, an important aspect of HIV infection management is cardiometabolic protection. There is short-term evidence supporting lifestyle intervention at HAART initiation and longer-term data are awaited. Until those data are available, every clinical effort should be made for early identification and intervention of diabetes and cardiovascular risk factors, with care on par with that expected in the general population.

Disclosure Conflicts of interest: K. Samaras: has been a consultant for MSD (sitaglitpin expert advisory committee); receives royalties from for *Fast Facts Diabetes*, Oxford Health Press; has received payment for development of educational presentations including service on speakers' bureaus as a speaker on obesity management; and has received travel/accommodations expenses covered or reimbursed from MSD (attendance at EASD, Lisbon, 20122).

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