Effect of Nonnucleoside Reverse Transcriptase Inhibitor–Based Antiretroviral Therapy on Dysglycemia and Insulin Sensitivity in South African HIV-Infected Patients

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Background: Data on the prevalence of the complications of antiretroviral therapy (ART) (diabetes, central fat accumulation, peripheral fat wasting, and dyslipidemia) in sub-Saharan Africa are sparse. We examined the prevalence and associated risk factors of dysglycemia and insulin sensitivity in HIV-infected South Africans.

Methods: HIV-infected patients, on nonnucleoside reverse transcriptase inhibitor–based ART or ART-naive, had oral glucose tolerance tests and clinical anthropometry. Insulin sensitivity and b-cell function were assessed.

Results: The prevalence of dysglycemia in 406 ART-naive patients and 443 patients on ART was 25.7% and 21.9% (P = 0.193), respectively. Dysglycemic patients on ART had a similar body mass index (P = 0.440), greater waist circumference (P = 0.047), and smaller calf skinfold thickness (P = 0.015) than dysglycemic ART-naive patients but no difference in b-cell function or insulin sensitivity. Normoglycemic patients on ART had a greater body mass index (P = 0.0009), waist circumference (P = 0.0001), and abdominal skinfold thickness (P = 0.040), similar calf skinfold thickness (P = 0.079), and reduced b-cell function [lower insulinogenic index (P = 0.027) and oral disposition index (D_o, P = 0.020)] compared with normoglycemic ART-naive patients. In multivariate analysis, older age [odds ratio (OR): 1.04, 95% confidence interval (CI): 1.02 to 1.06], male gender (OR: 1.96, 95% CI: 1.28 to 2.99), higher CD4 count (OR: 1.0, 95% CI: 1.00 to 1.02) and use of efavirenz (OR: 1.70, 95% CI: 1.19 to 2.45) were associated with dysglycemia.

Conclusions: The prevalence of dysglycemia in ART-naive and ART patients was similar. Peripheral fat wasting was more common in dysglycemic patients on ART. The association of efavirenz with dysglycemia is important because first-line ART regimens in the developing world include nonnucleoside reverse transcriptase inhibitors, and increasingly, efavirenz is selected because of its perceived lower toxicity than nevirapine.

Key Words: human immunodeficiency virus (HIV), diabetes, impaired glucose metabolism, dysglycemia, antiretroviral therapy

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INTRODUCTION

Sub-Saharan Africa accounts for 67% of HIV infections worldwide, 68% of new HIV infections among adults, 91% of new HIV infections among children, and 72% of the world's AIDS-related deaths.[1] Within the region, Southern Africa has had the highest burden of the HIV epidemic, and South Africa, with an estimated population of 5.7 million people living with HIV, has the largest population of HIV-positive people globally. In recent years, access to antiretroviral therapy (ART) has risen from approximately 2% of people who are in need of this therapy in 2003 to approximately 44% in 2008. In South Africa, approximately 930,000 people are receiving ART.[2] The well-recognized benefits of ART, which results in dramatic reductions in mortality and morbidity, may, however, be accompanied by the development of metabolic sequelae, including altered body composition (central fat accumulation and peripheral fat wasting), dysglycemia, and dyslipidemia.[3–5] Reports of these complications have predominantly come from industrialized countries, where ART regimens containing protease inhibitors are the mainstay of treatment.[6–8] More recently, nucleoside reverse transcriptase inhibitors (NRTIs), in particular stavudine (d4T), have been shown to increase insulin resistance.[9] The metabolic response to ART may be different in South Africans, where HIV-infected patients are predominantly young black women compared with middle-aged men

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from industrialized countries.[1] Black South African women, both lean and obese, are more insulin resistant than their white counterparts, despite having less visceral adiposity, suggesting different pathophysiologic processes.[10] Furthermore, environmental and socioeconomic factors, such as malnutrition, poverty, and chronic infections, as well as the initiation of ART at an advanced stage of the disease (CD4 lymphocyte count ,200 cells/mm^3), may influence the metabolic response to HIV and ART.

Therefore, the aims of the present study were to document the prevalence of dysglycemia in HIV-infected South African patients and to determine the impact of first-line ART [in South Africa, similar to most low- and middle-income countries, this consists of d4T or zidovudine (AZT), lamivudine (3TC), and efavirenz or nevirapine] on dysglycemia.

METHODS

Participants

HIV-infected patients on the South African National Department of Health first-line ART regimen (d4T, 3TC, and efavirenz or nevirapine) and those not yet on ART (ART-naive) were conveniently sampled consecutively from a list at a community health care center in Cape Town. Patients were excluded if they had a history of diabetes mellitus or impaired glucose tolerance (IGT), had been on ART for less than 6 months, had an active acute opportunistic infection, had severe diarrhea (.6 stools/d), had tuberculosis within 1 month of commencing treatment, had received glucocorticoid therapy within the past 6 months, or were pregnant or known to have renal failure. The study was approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. Before participating in the study, procedures and risks were explained to the subjects, who gave written informed consent to participate in the study.

Testing Procedures

Collection of Sociodemographic and Medical Details

Trained field workers administered a questionnaire to the participants to obtain data on sociodemographic details, known diabetes risk factors, family history, medical history, smoking, alcohol, and current medication. Subjects' clinical records were reviewed, and information was extracted on prior weight, ART regimen, time on ART, CD4 count, viral load, and renal function.

Blood Sampling and Measurement of Glucose Tolerance, Insulin Sensitivity, and B-Cell Function

After an overnight fast, subjects underwent a 75-g oral glucose tolerance test (OGTT), with venous blood samples taken at 0, 30, and 120 minutes for the measurement of plasma glucose and serum insulin concentrations. The plasma was stored at 220 before analysis of glucose concentrations, and the serum was stored at 280 C for the subsequent analysis of insulin concentrations.

b-Cell function was estimated using the insulinogenic index [IGI, calculated as the ratio of the change in insulin to the change in glucose from 0 to 30 min ($\Delta Insulin_{0-30}/\Delta Glucose_{0-30}$)], homeostatic model assessment (HOMA-b, 20 3 fasting insulin/fasting glucose 2 3.5), and the oral disposition index (D_o, a $\Delta Insulin_{0-30}/\Delta Glucose_{0-30}$ 3 1/fasting insulin).[11,12] Insulin resistance was estimated using the homeostatic model assessment (HOMA-IR, fasting glucose 3 fasting insulin/22.5).[12]

Seventy-seven subjects had a negative IGI ($\Delta I_{0-30}/\Delta G_{0-30}$) and were excluded from analyses, including this parameter.

Body Composition Assessment

Weight, height, circumferences (waist, hip, mid–upper arm and midthigh), and skinfold thickness (at the biceps, triceps, subscapular region, abdomen, suprailiac region, thigh, and calf) were taken as previously described in duplicate by a single trained investigator.[9] Sagittal abdominal diameter was measured as the distance between the blades of a portable sliding-beam caliper at the level of iliac crest (L4–5) after a normal expiration with the subject lying in the supine position on a flat, standard, clinic examining bed.

Biochemical Analyses

Plasma glucose concentrations were determined using the glucose oxidase method (ACE Alera Clinical Chemistry System, Alfa Wassermann Diagnostic Technologies, Woerden, Netherlands). Serum insulin concentrations were determined by immunochemiluminometric assays using the ADVIA Centaur (Bayer Diagnostics, Tarrytown, New York). The intraassay and interassay coefficients of variation for plasma glucose and serum insulin concentrations were 2.5% and 3.7%, and 4.5% and 12.2%, respectively.

Definitions

1. Diabetes: fasting plasma glucose (FPG) $7 mmol/L or 2-hour plasma glucose during the OGTT $11.1 mmol/L.
2. Prediabetes: 2-hour plasma glucose during the OGTT $7.8 mmol/L but ,11.1 mmol/L (IGT) or FPG $5.6 mmol/L but ,7.0 mmol/L [impaired fasting glucose (IFG)].
3. Dysglycemia: prediabetes or diabetes.
4. Normal glucose tolerance: FPG ,5.6 mmol/L or a 2-hour plasma glucose during the OGTT ,7.8 mmol/L.[13]

Statistical Analyses

All data were presented as medians and interquartile range. The prevalence of dysglycemia between treatment groups was compared using a x^2 analysis. Missing data were imputed. For the analysis of the third drug (efavirenz or nevirapine), patients were excluded if they had changed their third drug during the course of their treatment. Logistic regression models were fitted to determine factors associated with dysglycemia. Variables found significant (P , 0.05) in univariate analysis were included in the final multivariate model. All tests were 2 sided. SPSS Version 18 and Statistica Version 10 were used to perform the analyses.

RESULTS

Subject Characteristics

Of the 1232 patients recruited, 383 were excluded [307 consented but did not attend for testing, 51 had missing data,

25 had technical difficulties (laboratory or venesection)], leaving 849 patients for analysis (443 on ART and 406 on ART-naive). Patients with dysglycemia were older (P = 0.0001), more likely to be male (P = 0.0001), have higher CD4 counts (P = 0.0002), have a lower housing density (P = 0.033), and, in those on ART, were more likely to be taking efavirenz as the third drug (P = 0.0001). The normoglycemic and dysglycemic groups were otherwise similar for level of education, previous/current tuberculosis, taking ART, and duration on ART (Table 1).

Of the patients on ART (n = 443), 66.8% were currently taking d4T, 33.2% were on AZT, 100% were on 3TC, 46.3% were on nevirapine, and 53.7% were on efavirenz. Those on ART had been on treatment for a median of 16 months. Patients were only included if they had been on ART for $6 months. The most frequent change was the substitution of d4T with AZT, hence not all patients on AZT had been on the drug for $6 months.

Prevalence of Dysglycemia

The combined prevalence of dysglycemia did not differ between the ART-naive and ART groups (Table 2, P = 0.193). Patients who had only ever received efavirenz as the third drug had a higher prevalence of dysglycemia compared with those who had only ever received nevirapine (73% vs 27%, P = 0.0001, Table 1).

TABLE 1. Characteristics of Those Patients Who Were Normoglycemic (NGT) and Those Who Were Dysglycemic (Dys)

	NGT	Dys	P
Number (n)	646	203	—
Age, yr	32 (28–38)	37 (32–44)	0.0001
Gender			0.0001
Male	130 (20)	66 (33)	
Female	516 (80)	137 (67)	
Education			0.102
Primary	147 (22.8)	60 (29.6)	
Secondary	245 (37.9)	76 (37.4)	
Tertiary	254 (39.3)	67 (33.0)	
Housing density (persons/room)	2.0 (1.0–3.0)	1.5 (1.0–2.5)	0.033
Tuberculosis (previous/current)	307 (48.6)	113 (56.5)	0.051
CD4 count (cells/mL)	279 (174–435)	345 (220–514)	0.0002
ART			0.193
No	317 (49)	89 (44)	
Yes	329 (51)	114 (56)	
Treatment regimen			
Drug 1			0.233
d4T	225 (68)	71 (62)	
AZT	104 (32)	43 (38)	
Drug 2			—
3TC	329 (100)	114 (100)	
Drug 3			0.0001
Efavirenz	155 (47)	83 (73)	
Nevirapine	174 (53)	31 (27)	
Duration on treatment (mo)			
d4T	12.0 (8–19)	14 (9–22)	0.084
AZT	11.5 (6–20)	14 (8–17)	0.418

Data presented as median (interquartile range) or number (percentage).

TABLE 2. Prevalence of Dysglycemia in Patients on ART and ART-Naive Patients

	n	NGT	Pre-DM	DM
Naive, n (%)	406	317 (78.1)	75 (18.5)	14 (3.4)
ART, n (%)	443	329 (74.3)	104 (23.5)	10 (2.2)
P	—	0.173	0.074	0.292

Body Composition

Dysglycemic patients on ART had a greater centralization of fat [greater waist circumference (P = 0.047) and waist:hip ratio (P = 0.009)] but more peripheral wasting in the lower limbs [smaller calf skinfold thickness (P = 0.015)] than ART-naive dysglycemic patients (Table 3). Normoglycemic patients on ART also had a greater centralization of fat [waist circumference (P = 0.0001), waist:hip ratio (P = 0.0001), and abdominal skinfold thickness (P = 0.040)], but this was accompanied by a higher body mass index (BMI) (P = 0.0009) and no significant peripheral wasting [smaller calf skinfold thickness (P = 0.079)] (Table 3) than normoglycemic ART-naive patients.

When comparing dysglycemic with normoglycemic patients on ART, the dysglycemic patients had a greater centralization of fat [waist circumference (P = 0.002) and waist:hip ratio (P = 0.0001)] and more peripheral wasting [smaller skinfold thickness at the triceps (P = 0.031), thigh (P = 0.047), and calf (P = 0.003)] (see Table, Supplemental Digital Content 1, http://links.lww.com/QAI/A174). In contrast, when comparing the dysglycemic and normoglycemic ART-naive patients, the dysglycemic patients had a greater centralization of fat [greater waist circumference (P = 0.002), waist:hip ratio (P = 0.0001), and abdominal skinfold thickness (P = 0.005)] but no peripheral wasting (see Table, Supplemental Digital Content 1, http://links.lww.com/QAI/A174).

Glucose and Insulin Dynamics

Dysglycemic patients on ART had a lower 2-hour plasma glucose (P = 0.018) than dysglycemic naive patients (Table 4), but there were no differences in HOMA-IR, HOMA-β, IGI, or D_o in these patients. In contrast, normoglycemic patients on ART had a higher FPG (P = 0.0004), IGI (P = 0.027), and D_o (P = 0.020) than normoglycemic ART-naive patients.

When comparing dysglycemic with normoglycemic patients on ART, the dysglycemic patients were more insulin resistant [greater HOMA-IR (P = 0.0001)], had reduced β-cell function [lower HOMA-β (P = 0.036) and IGI (P = 0.001)], and had a lower D_o (P = 0.0001) (see Table, Supplemental Digital Content 2, http://links.lww.com/QAI/A175). Results were similar when comparing dysglycemic with normoglycemic ART-naive patients (see Table, Supplemental Digital Content 2, http://links.lww.com/QAI/A175).

TABLE 3. Body Composition and Regional Fat Distribution Between Normoglycemic (NGT) and Dysglycemic (Dys) Patients

	NGT			Dys		
	Naive	ART	*P*	Naive	ART	*P*
Number (n)	317	329	—	89	114	—
BMI (kg/m^2)	23.9 (21.3–28.2)	25.4 (22.8–29.4)	0.0009	25.6 (22.7–30.8)	26.4 (23.1–30.8)	0.440
Measurements						
Waist (cm)	80.0 (73.5–87.5)	83.8 (77.0–93.3)	0.0001	83.5 (76.5–95.0)	88.3 (79.8–98.5)	0.047
Waist:hip	0.83 (0.78–0.88)	0.86 (0.80–0.91)	0.0001	0.87 (0.82–0.92)	0.90 (0.85–0.94)	0.009
Skinfolds						
Abdomen (mm)	16.6 (10.8–28.0)	19.8 (12.3–29.5)	0.040	23.5 (12.6–35.3)	23.6 (11.3–31.0)	0.440
Triceps (mm)	14.8 (9.4–22.1)	15.30 (9.6–22.6)	0.584	15.7 (8.7–23.7)	13.6 (7.0–19.3)	0.056
Thigh (mm)	27.1 (14.1–41.5)	25.5 (15.9–38.5)	0.683	28.0 (14.0—41.90)	20.7 (11.2–35.5)	0.144
Calf (mm)	15.5 (9.7–22.8)	14.5 (8.4–21.1)	0.079	15.9 (7.9–21.5)	10.6 (6.2–17.9)	0.015

In a univariate analysis, older age (P = 0.0001), male gender (P = 0.0001), higher CD4 count (P = 0.0001), greater BMI (0.005), greater waist circumference (P = 0.0001), and use of efavirenz (P = 0.0001) were significantly associated with dysglycemia (Table 5). However, in a multivariate model, only older age (P = 0.0001), male gender (P = 0.002), higher CD4 count (P = 0.003), and use of efavirenz (P = 0.004) remained significant (Table 5).

DISCUSSION

This is the largest study from a developing country to use insulin and glucose levels derived from an OGTT to examine the prevalence of dysglycemia and its predictors and measures of insulin sensitivity and b-cell function in HIV-infected patients. We describe for the first time a significant association between the use of efavirenz and dysglycemia. We also report a similar prevalence of dysglycemia in ART-naive patients and those on a nonnucleoside reverse transcriptase inhibitor (NNRTI)–based ART regimen and central fat accumulation but more peripheral fat wasting in dysglycemic patients on ART.

There is a paucity of data on the prevalence of impaired glucose metabolism in HIV-positive patients in Africa and most studies have used fasting glucose as the sole measure to define dysglycemia. Consequently, they are likely to have underestimated the prevalence. Despite this limitation, a cross-sectional study from Rwanda (n = 150) and a longitudinal study from Benin (n = 79) demonstrated a high prevalence (34–37%) of IFG (defined as a FPG .5.6 mmol/L) in HIV-positive patients on ART.[14,15] In contrast, a larger study from Kenya, using an OGTT to define dysglycemia, reported a low prevalence of IFG (ART, 2.2%; ART-naive, 0.6%) and diabetes (ART, 1.5%; ART-naive, 1.2%) but a high prevalence of IGT (ART, 16.4%; ART-naive, 21.1%).[16] Our prevalence of dysglycemia is thus similar to that shown in the Kenyan study, and, interestingly, both studies show that ART-naive patients have a similar prevalence of dysglycemia compared with those on ART.

In our study, although the BMI was similar in ART patients with dysglycemia and those with normal glucose tolerance, the fat distribution was different in that the dysglycemic patients had significantly more visceral adiposity (higher waist circumference but similar abdominal skinfold thickness) and peripheral wasting. These data suggest that increased visceral adiposity and peripheral fat wasting (mixed-type lipodystrophy) are associated with dysglycemia. Time on ART was not significantly different between the 2 groups, suggesting that there are probably factors other than duration on ART that increase the susceptibility of patients to central fat accumulation and peripheral fat wasting. In contrast, in the ART-naive patients, those with dysglycemia were overweight (higher BMI), with more visceral and superficial abdominal adiposity (greater waist circumference and abdominal skinfold thickness) but no peripheral wasting.

In a univariate model, older age, male gender, higher CD4 count, higher BMI, greater waist circumference, and use

TABLE 4. Glycemic Parameters Between Normoglycemic (NGT) and dysglycemic (Dys) patients

	NGT			Dys		
	Naive	ART	*P*	Naive	ART	*P*
Number (n)	317	329	—	89	114	—
Fasting glucose (mmol/L)	4.8 (4.5–5.1)	4.9 (4.7–5.2)	0.0004	5.9 (5.6–6.3)	5.9 (5.7–6.3)	0.565
2hr glucose (mmol/L)	5.3 (4.7–6.1)	5.2 (4.7–5.9)	0.293	7.8 (6.4–8.7)	6.6 (5.8–8.1)	0.018
Fasting insulin (mIU/L)	4.5 (3.0–6.9)	4.5 (2.6–7.3)	0.495	5.5 (3.2–9.6)	6.1 (3.1–12.8)	0.467
HOMA-IR	0.95 (0.6–1.5)	1.0 (0.6–1.6)	0.741	1.35 (0.8–2.6)	1.7 (0.8–3.3)	0.367
HOMA-beta	73.7 (46.6–111.5)	64.8 (36.9–104.6)	0.051	47.7 (28.0–84.0)	50.1 (27.7–98.6)	0.636
IGI	19.1 (10.1–32.6)	23.8 (10.6–44.9)	0.027	13.0 (6.7–22.5)	14.3 (6.0–26.7)	0.257
D_o	4.2 (2.6–7.4)	4.9 (2.6–10.6)	0.020	2.3 (1.2–3.5)	2.4 (1.1–5.2)	0.346

TABLE 5. Univariate and Multivariate Analyses of Factors Determining Dysglycemia

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (yr)	1.060	1.04 to 1.08	0.0001	1.044	1.02 to 1.06	0.0001
Male	1.912	1.34 to 2.71	0.0001	1.956	1.28 to 2.99	0.002
CD4 count (cells/mL)	1.001	1.001 to 1.002	0.0001	1.001	1.00 to 1.02	0.003
BMI (kg/m^2)	1.037	1.01 to 1.06	0.005	1.002	0.94 to 1.07	0.944
Waist (cm)	1.031	1.02 to 1.04	0.0001	1.025	0.99 to 1.06	0.138
Efavirenz	2.321	1.66 to 3.25	0.0001	1.704	1.19 to 2.45	0.004

CI, confidence interval; OR, odds ratio.

of efavirenz were significantly associated with dysglycemia. However, after multivariate analysis, only older age, male gender, higher CD4 count, and use of efavirenz remained significant. The higher BMI and greater waist circumference were most likely accounted for by the subjects with higher CD4 counts, possibly indicating patients with less immunosuppression and better health, as patients with lower CD4 counts often have more advanced HIV infection. Efavirenz contributing to the higher BMI and greater waist circumference cannot be excluded.[17]

Our finding that efavirenz, as part of the first-line therapy, was independently associated with dysglycemia has not previously been reported and is important as first-line ART regimens in the developing world are based on NNRTIs, and, increasingly, efavirenz is selected because of its perceived lower toxicity than nevirapine. Martinez et al[18] showed that, in patients on a dual-NRTI–based regimen and a protease inhibitor, if the protease inhibitor is replaced with nevirapine, efavirenz or abacavir, there is a significantly higher FPG in those patients taking efavirenz.[18] Although their findings are supportive of ours, efavirenz was not used as a first-line therapy in their study, and the contribution of previous exposure to a protease inhibitor (PI) to the development of a higher fasting glucose is unknown. In contrast, Dube et al[19] showed no significant change in glycemia and peripheral limb fat when efavirenz was added to an NRTI-based regimen, and Fisac et al[20] demonstrated that in HIV-infected patients in whom a protease inhibitor was substituted with efavirenz, despite there being a small but significant increase in FPG and a significant decrease in fasting serum insulin levels, there was an insignificant change in the degree of insulin resistance. In addition, in the Swiss HIV Cohort Study, Ledergerber et al[21] demonstrated that treatment with NRTIs plus NNRTIs was not associated with a significantly increased incidence of type 2 diabetes in HIV-infected individuals (Incidence rate ratio [IRR], 1.47; 95% confidence interval: 0.77 to 2.82). Efavirenz has been linked to the development of lipodystrophy, especially if used with thymidine analogs, such as d4T, which is thought to be due to the inhibition of lipogenesis or altered adipocyte differentiation.[22] Interestingly, Cameron et al[23] showed that an efavirenz-based regimen caused significantly more peripheral lipoatrophy than a lopinavir/ritonavir-based regimen, yet there were no changes in glucose tolerance in the 2 groups. This is different to our study, where we have shown that those with dysglycemia have more peripheral wasting. Whether the dysglycemia in patients taking efavirenz in this study is part of the lipodystrophy syndrome or due to its combination with d4T remains to be elucidated. As few patients were not taking d4T or had previously not been exposed to d4T (of the 230 patients currently taking AZT, 222 had previously been on d4T) and 3TC, the independent effect of these drugs on dysglycemia could not be adequately assessed.

In this cross-sectional study, it is not possible to determine the mechanisms underlying the dysglycemia, although these are likely to be multifactorial. First, d4T has been implicated in dysglycemia by altering mitochondrial function and reducing insulin sensitivity.[24] Second, there is a greater centralization of fat and marked peripheral fat wasting in patients on ART, suggesting the presence of a mixed-type lipodystrophy. Peripheral fat wasting is well described in patients on d4T, whereas central fat accumulation is associated with the use of 3TC, efavirenz, and nevirapine.[17,22,25] A different phenotype is seen in the dysglycemic ART-naive patients who are overall more overweight than the normoglycemic ART-naive patients, possibly suggesting a different mechanism for the dysglycemia in these 2 patient groups. Third, the older age may have contributed to the development of dysglycemia in those patients on ART. Finally, there may also be a direct viral effect in individuals already predisposed to dysglycemia.

Limitations of our study include the lack of an HIV-negative control group, the relatively short duration of exposure to ART, the relatively few number of males, which is largely representative of the greater prevalence of HIV infection in females in sub-Saharan Africa, and the cross-sectional design that limits the assessment of causation. In addition, because we excluded patients known to already have diabetes or prediabetes, we may have underestimated the prevalence of dysglycemia due to HIV infection or ART. However, despite these limitations, this study contributes a number of novel findings: (1) it has the largest sample of HIV-positive patients from sub-Saharan Africa with metabolic sequelae, (2) it highlights the possibility of a different mechanism for dysglycemia in patients taking ART compared with ART-naive patients, (3) it provides evidence for peripheral wasting with metabolic sequelae in those taking ART, and (4) it provides evidence for drug regimen–specific effects, with efavirenz, the main culprit, as the third of the 3-drug regimen.

In conclusion, we show that patients on ART have a greater centralization of fat and more peripheral wasting, without a higher prevalence of dysglycemia compared with

ART-naive patients. Our intriguing finding that efavirenz was associated with dysglycemia requires further exploration. Whether this picture changes with longer exposure to ART is currently being assessed in a longitudinal study.