High rates of incident diabetes and prediabetes are evident in men with treated HIV followed for 11 years

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Objective: To determine the long-term incidence of glucose disorders in treated HIV infection, associations with traditional and HIV-specific risk factors.

Methods: Observational cohort of 104 men with treated HIV infection and without diabetes, aged 43 ± 8 years at baseline, with (mean ± SD) 11.8 ± 3.5 years follow-up. Ascertainment of glucose status by fasting glucose or, in a subset ($n = 33$), a 75 g oral glucose tolerance test by 10–12 years follow-up. A subset underwent sequential body composition measures ($n = 58$) to determine changes in total body and central abdominal adiposity.

Results: The cumulative incidence of glucose disorders was 45.8% (prediabetes 32.3%, diabetes 12.5%), with an incidence rate of 34.5/1000 years of patient follow-up (PYFU) (prediabetes: 24.3/1000 PYFU; diabetes: 10.2/1000 PYFU). Incident glucose disorders were independently associated with higher age (44.9 ± 8.4 vs. 41.1 ± 7.5 years, $P = 0.027$), baseline C-peptide (2.9 ± 1.3 vs. 2.4 ± 1.1 ng/ml, $P = 0.019$) and baseline 2-h glucose (135 ± 41 vs. 95 ± 25 mg/dl, $P < 0.001$). A prior AIDS-defining illness was independently associated with higher follow-up fasting glucose (108 ± 38 vs. 94 ± 16 mg/dl, $P = 0.007$). Abdominal fat gain over 2–4 years was associated with a 3.16-fold increased risk of incident glucose disorders (95% CI 1.30–7.68, $P = 0.011$). In a subgroup who underwent further oral glucose tolerance testing, 60% had a glucose disorder, the majority not detected by fasting glucose.

Conclusion: Men with long-term treated HIV infection have high rates of incident glucose disorders associated with modest abdominal fat gain. Directed measures to prevent diabetes in this population are warranted.

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Introduction

HIV infection currently affects 36.7 million people worldwide [1]. The introduction of combined antiretroviral therapy (cART) has dramatically transformed the natural history of HIV infection and the lives of people living with it, impacting the development of AIDS, life expectancy and quality of life. In 2017, approximately 20.9 million people globally were receiving cART [1]. These benefits are, however, at the cost of cART-associated cardiometabolic consequences that include diabetes mellitus (diabetes) [2–5]. These appear to be increased by cumulative exposure, especially with the early nucleoside reverse transcriptase inhibitors (NRTIs) [6–8]. Notably, early NRTIs are most strongly implicated in the pathogenesis of HIV-related lipodystrophy [8]. Although these medications are infrequently prescribed in resource-rich countries today, they may still be first-line in some resource-limited settings where the highest prevalence of HIV infection exists.

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There are few long-term studies reporting the incidence of diabetes in people living with treated HIV infection. The longest study to date, with up to 10 years follow-up, reported an incidence of 14.1 cases/1000 patient-years follow-up (PYFU) [9]. Three shorter term studies reported lower incidence rates [8,10,11]. The Data Collection on Adverse Event of Anti-HIV Drugs (D:A:D) reported incident diabetes at 5.72/1000 PYFU in 33 389 HIV-infected people over 3.8 years [8]. Other studies of 4–7 years follow-up reported incidence rates of 4.4–5.0/1000 PYFU [10,11]. Further, changes in diabetes incidence are evident over time, at least in HIV-infected youth [12], where a near 10-fold increase in incidence has been observed: from 0.15/1000 PYFU in 2000–2007 to 1.67/1000 PYFU subsequently [12].

Risk factors for diabetes in treated HIV infection include older age [9,11], higher BMI [8,9,11], lipodystrophy [5,9], dyslipidaemia [8,9,11], and exposure to stavudine [8,9], zidovudine [8], didanosine [8,9], and indinavir [9]. Whilst differences in age, cART exposures and observation duration may explain some of the incidence rate differences in prior studies, much remains unclear about factors, which may promote diabetes risk in HIV infection, particularly the impact of the obesity epidemic.

In this study, we determined the long-term incidence of diabetes and prediabetes in a cohort of men with treated-HIV infection who, in 1997, underwent detailed phenotyping for a study examining the natural history of lipodystrophy [13]. Baseline factors were examined for their association with long-term incident glucose disorders.

Methods

Patients

This prospective cohort study (St Vincent's HIV and Diabetes Study) examined baseline data from 144 HIV-infected men recruited between August and September 1997 for metabolic complication evaluation [13]. Figure 1 shows participation and drop-outs, assessments and inclusion for longer term follow-up. Long-term follow was defined as at least 2 years, and ranged up to 18 years. Of 144 participants, 36 had less than 2 years follow-up ('drop outs') and were excluded, as were four participants with known diabetes at baseline. Therefore, data are presented on 104 participants.

The cohort is unique, in that the majority of original participants continue attendance at St Vincent's Hospital for HIV-infection management, at least in part because of their demographics: predominantly inner-city men who have sex with men, mostly well educated, all receiving cART at baseline and committed to receiving regular HIV-infection ambulatory care. The protocol was approved by the Research Ethics Committee of St Vincent's Hospital. All patients provided written informed consent.

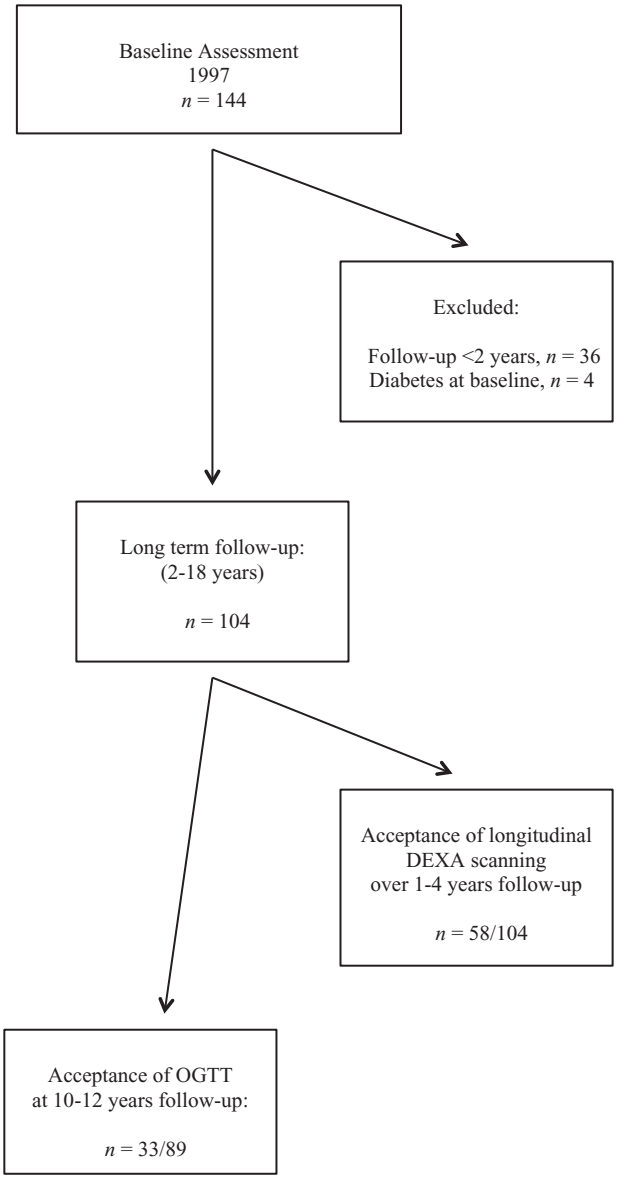

Fig. 1. Flow chart for participants in the St Vincent's HIV and Diabetes Study.

Assessments

Baseline data were collected in 1997 on age, known HIV-infection duration, prior AIDS-defining illness, clinical presence of lipodystrophy, weight, height, $CD4^+$ lymphocyte count and HIV viral load, previously described [13]. Baseline blood was collected in 1997 following a 12-h overnight fast with measurement of glucose, insulin, C-peptide, lipids, testosterone, cortisol, leptin and tumor necrosis factor-α (TNFα), followed by a 75 g oral glucose tolerance test (OGTT) [13]. Insulin resistance and secretion were estimated using the

homeostasis model assessment, as described [13]. Case records were reviewed to ascertain all fasting glucose measurements.

Follow-up duration was determined by the date of the last fasting glucose measurement. At approximately 10–12 years after the baseline assessment, all participants attending HIV-ambulatory care were invited to undertake a 75 g OGTT.

Ascertainment of incident glucose disorders and incident diabetes

As our early work established high rates of premature diabetes in this cohort [13], routine care for HIV-infection treatment included fasting glucose levels. Routine clinic visits for HIV-infection treatment review occurred approximately every 6 months (Fig. 1). Long-term glucose status was available in 104 (74%); 75/104 participants had fasting glucose levels alone and 33/104 randomly selected participants underwent a later OGTT. Follow-up glucose status was classified as normal fasting glucose, prediabetes [impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)] or diabetes, using the American Diabetes Association criteria [14]. Prediabetes was defined as two fasting plasma glucose levels of 100–125 mg/dl (5.6–6.9 mmol/l) and/or 2-h plasma glucose of 140–199 mg/dl (7.8–11.0 mmol/l) following a OGTT. Diabetes was defined as two fasting plasma glucose levels at least 126 mg/dl ($\geq$7 mmol/l) and/or a 2-h plasma glucose at least 200 mg/dl ($\geq$11.1 mmol/l) following a OGTT.

Incident diabetes was defined as a new diagnosis of diabetes using the above criteria or a physician-diagnosis of diabetes subsequent to the baseline visit. A second categorical variable of incident glucose disorders was defined as either incident diabetes or prediabetes.

Exposure to cART medications was determined by medical record examination.

Baseline physical activity was measured by a validated questionnaire, detailing physical activity over the preceding 12 months, as described [15].

All patients were invited to undertake body composition scanning for measurement of total body and abdominal fat using dual-energy X-ray absorptiometry (DEXA); 85 patients had at least one measure; 58 had subsequent measures at 12 months, then annually for up to 2–4 years. Longitudinal changes in total and abdominal fats were defined as early term (baseline to 12 months) and medium term (baseline to 2–4 years) using the last data available.

Statistical analyses

Between-group comparisons were performed using analysis of variance (ANOVA) for normally distributed continuous variables, the Mann–Whitney test for nonnormally distributed variables and contingency tables with the chi-square statistic for categorical variables.

Incidence rates for prediabetes, diabetes and all glucose disorders were determined by dividing the new cases by the duration of follow-up, multiplied by 1000.

Cox regression analysis was used to determine the risk of incident glucose disorders and incident diabetes. The censor date was the date of the last normal glucose level on record; the event date was the date of the first glucose level that ascertained an incident glucose disorder or diabetes. The base model included age, known HIV-infection duration, BMI and prior AIDS as covariates. Baseline metabolic characteristics were singly added into the base model in separate analyses.

Cox regression analyses also examined the risk of early-term and medium-term gains in abdominal fat on risk of incident glucose disorders. In these analyses, covariates included age, prior AIDS, and the identified metabolic risk predictors of baseline fasting glucose and C-peptide. Cox regression analyses for incident diabetes were not undertaken in the serial body composition data subgroup, as there were only five incident cases with diabetes.

Further Cox regression analyses were undertaken entering medication exposure. Exposure to each type of medication was entered as a binary variable, each added singly into separate analyses where the base model included age, BMI, prior AIDS, known HIV-infection duration.

Survivor bias was assessed by comparing participants in follow-up with those who dropped out before 2 years, using ANOVA for normally distributed continuous variables, the Mann–Whitney test for nonnormally distributed variables and contingency tables with the chi-square statistic for categorical variables. Using the same approach, survivor bias was further interrogated by comparing data of participants with 2–9.9 years of follow-up with those with 10–18 years of follow-up.

Selection bias in participant acceptance of the OGTT at 10–12 years follow-up was assessed by comparing the baseline characteristics using ANOVA for normally distributed continuous variables, Mann–Whitney test for nonnormally distributed variables and contingency tables with the chi-square statistic for categorical variables. Selection bias was similarly assessed in the subgroup who underwent serial body composition measures.

A significant P value for all analyses was defined at less than 0.05. All analyses were performed using SPSS (Version 23; IBM Corp., Armonk, New York, USA).

Results

Patients

Of the original 144 participants, four had diabetes at baseline and were excluded; 36 had dropped out of HIV ambulatory clinic care and 104 had long-term glucose levels available. Baseline characteristics are shown in Table 1: mean (±SD) age 42.9 ± 8.2 years, BMI 24.3 ± 2.6 kg/m^2, known HIV-infection duration 8.4 ± 4.1 years; 30% had a prior AIDS-defining illness ($n = 32$). The mean glucose was 4.9 ± 0.6 mmol/l; 96 had normal fasting glucose, 8 had IFG. Follow-up was 11.8 ± 3.4 years (median 12.8 years). Baseline characteristics were similar between participants with long-term follow-up and those who dropped out of HIV ambulatory clinics before 2 years, apart from lower rates of lipodystrophy in the latter (Supplementary Table 1, http://links.lww.com/QAD/B198). Baseline characteristics were also similar between participants with 2–10 years follow-up compared with those with more than 10 years follow-up (Supplementary Table 2, http://links.lww.com/QAD/B198).

During the follow-up period, 50 participants developed a new glucose disorder (45.8%): prediabetes in $n = 37$ (32.3%) and type 2 diabetes in $n = 13$ (12.5%). The incidence of glucose disorders was 34.5/1000 PYFU: prediabetes 24.3/1000 PYFU and diabetes 10.2/1000 PYFU. Figure 2 shows the cumulative incidences of glucose disorders and diabetes.

Detection of incident glucose disorders was further examined in a subgroup who accepted the invitation for an OGTT at 10–12 years follow-up ($n = 33$, 32%). Participants who accepted the OGTT were similar to those who did not, for all baseline demographics (Supplementary Table 3, http://links.lww.com/QAD/B198). The OGTT identified incident glucose disorders in 61% ($n = 20$): IGT in 45% ($n = 15$) and diabetes in 15% ($n = 5$). Of 29 OGTT participants with normal fasting glucose at the time of the OGTT, IGT was identified in $n = 13$ (45%) and diabetes in $n = 3$ (10.3%). Of four OGTT participants with IFG at follow-up, higher-level glucose disorders were identified in all: IGT in $n = 2$ (50%) and diabetes in $n = 2$ (50%). In contrast, detection of glucose disorders was lower in participants not electing to undertake the OGTT at 10–12 years: incident glucose disorders (IFG or diabetes) in 31%; incident diabetes in 9% and no ability to detect IGT.

Data on the subgroup who elected to undertake longitudinal body composition measures are shown in Table 2 ($n = 58$). Participants who undertook body composition scanning were similar to those who did not, in age, BMI, known HIV-infection duration, baseline fasting glucose, CD4$^+$ cell counts and viral load, but had

Table 1. The Sydney St Vincent's Hospital HIV and Diabetes Study: baseline characteristics.

	Normal fasting glucose at follow-up ($N = 54$)	Incident glucose disorders ($N = 50$)	P^c
Baseline demographics			
Age (years)	41.2 ± 7.7	44.8 ± 8.4	0.027
Weight (kg)	75.8 ± 10.3	75.0 ± 8.8	0.66
BMI (kg/m^2)	24.4 ± 2.7	24.3 ± 2.4	0.94
Known HIV-infection duration (years)			
At baseline	8.3 ± 3.9	8.6 ± 4.4	0.71
At follow-up	18.4 ± 5.1	20.7 ± 5.8	0.035
Viral load (copies/ml)	3.2 ± 0.9	3.0 ± 0.9	0.38
CD4$^+$ cell count (cells/μl)	458.2 ± 227.3	467.7 ± 353.6	0.87
Lipodystrophy *n* (%)	42 (77.8%)	40 (80%)	0.49
Baseline metabolic measures			
Fasting glucose (mg/dl)	88 ± 14	88 ± 9	0.90
2-h glucose[a] (mg/dl)	95 ± 25	135 ± 41	<0.001
Fasting insulin (mU/l)	8.9 ± 4.2	9.3 ± 6.2	0.57
Insulin resistance [b]	2.0 ± 1.1	2.0 ± 1.3	0.60
Insulin secretion [b]	154.6 ± 147.3	137.0 ± 83.3	0.47
C-peptide (ng/ml)	2.4 ± 1.1	2.9 ± 1.3	0.019
Total cholesterol (mg/dl)	228 ± 70	232 ± 73	0.79
HDL cholesterol (mg/dl)	46 ± 15	43 ± 12	0.29
LDL cholesterol (mg/dl)	159 ± 62	159 ± 43	0.84
Triglycerides (mg/dl)	257 ± 292	310 ± 540	0.25
Leptin (ng/ml; $n = 66$)	3.4 ± 5.3	2.8 ± 1.8	0.49
Cortisol (μg/dl)	14.54 ± 5.15	14.61 ± 5.40	0.94
Testosterone (ng/dl; $n = 62$)	646 ± 412	602 ± 196	0.59
TNFα (pg/ml; $n = 55$)	3.9 ± 1.9	3.8 ± 1.4	0.89
Physical activity score (mets) ($n = 56$)	152 ± 56	165 ± 79	0.49

For nonnormally distributed variables (fasting insulin, insulin resistance, C-peptide and triglycerides), comparisons were by the Mann–Whitney test. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol. Conversion factors to SI units: glucose: ×0.0555; total, HDL and LDL cholesterol: ×0.0259; triglycerides ×0.0113; cortisol ×27.588; testosterone: ×0.0347.
[a]Following a 75 g oral anhydrous glucose load.
[b]Estimated using the Homeostasis Model Assessment [13].
[c]Comparisons for all normally distributed variables were by analysis of variance.

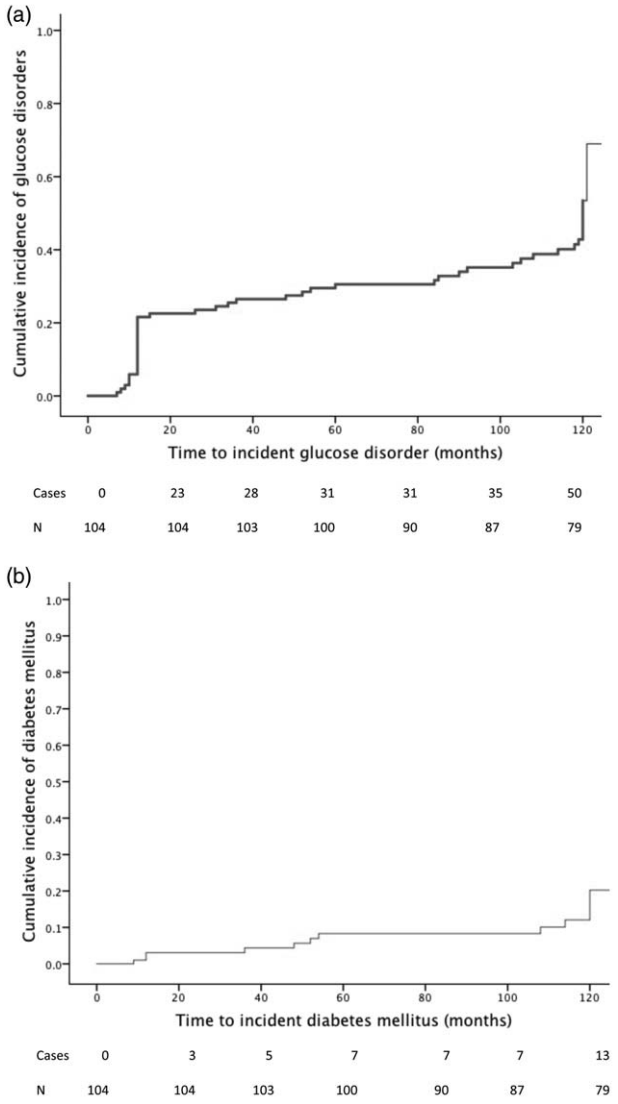

Fig. 2. Cumulative incidence of glucose disorders (a) and diabetes mellitus (b) in the Sydney St Vincent's Hospital HIV and Diabetes Study.

slightly longer follow-up duration (Supplementary Table 4, http://links.lww.com/QAD/B198).

There were no differences between those who developed incident glucose disorders to those who did not in baseline total body fat, limb fat, abdominal fat and lean tissue mass (Table 3). Changes in BMI and body composition were examined between the groups over the short-term (12 months) and medium term (2–4 years). Incident glucose disorders were associated with significantly greater short-term and medium-term gains in abdominal fat, with mean differences of approximately 230 and 320 g, respectively. Changes in BMI or total body fat in the short-term or medium-term were similar between the groups.

In Cox regression models, age was significantly and independently associated with risk for incident glucose disorders and diabetes, with a trend was observed for the presence of an AIDS-defining illness at baseline (Table 3).

Separate analyses added single baseline metabolic parameters to the model which included age, BMI, HIV duration and AIDS-defining illness. The hazard ratios for incident glucose disorders were significantly increased for higher baseline fasting glucose, 2-h glucose and C-peptide levels (Table 3). Baseline high density lipoprotein (HDL)-cholesterol, triglycerides, fasting insulin, insulin resistance and lipodystrophy presence were not associated with higher risk of incident glucose disorders in the long-term.

Similarly, the risk of incident diabetes was increased approximately five-fold by higher baseline fasting glucose, 2-h glucose and C-peptide levels; other metabolic or clinical parameters showed no increased risk (Table 3).

Separate Cox regression analyses examined the association between longitudinal abdominal fat gain and incident glucose disorder, with age, AIDS, baseline

Table 2. Weight, BMI and body composition in the subgroup undertaking serial dual-energy X-ray absorptiometry.

	Incident glucose disorders			Incident diabetes		
	No ($n=24$)	Yes ($n=34$)	*P*	No ($n=53$)	Yes ($n=5$)	*P*
Weight (kg)	75.8 ± 1.4	75.0 ± 1.3	0.66	75.4 ± 1.0	75.1 ± 2.6	0.91
BMI (kg/m^2)	23.8 ± 0.4	24.0 ± 0.5	0.74	23.8 ± 0.3	24.8 ± 2.4	0.41
Total fat (kg)	15.7 ± 1.1	16.3 ± 1.1	0.72	16.2 ± 0.8	14.9 ± 2.5	0.61
Total fat (%)	21.2 ± 1.2	21.6 ± 1.0	0.83	21.6 ± 0.8	20.0 ± 2.7	0.53
Limb fat (kg)	5.2 ± 0.5	5.1 ± 0.5	0.90	5.2 ± 0.4	4.8 ± 1.5	0.74
Abdominal fat (kg)	1.43 ± 0.09	1.49 ± 0.07	0.58	1.47 ± 0.06	1.41 ± 0.12	0.75
Lean tissue mass (kg)	56.8 ± 1.4	55.7 ± 0.9	0.49	55.9 ± 0.8	58.1 ± 2.1	0.38
Early-term changes (over 12 months)						
ΔBMI (kg/m^2)	-0.2 ± 0.2	0.2 ± 0.2	0.25	0.1 ± 0.1	-0.7 ± 1.1	0.13
ΔTotal fat (kg)	-1.4 ± 0.7	0.2 ± 0.7	0.09	-0.3 ± 0.5	-2.1 ± 1.1	0.25
ΔAbdominal fat (g)	-120 ± 59	108 ± 57	0.009	19 ± 47	-44 ± 112	0.67
Medium-term changes (2–4 years)						
ΔBMI (kg/m^2)	0.2 ± 0.2	0.7 ± 0.3	0.14	0.4 ± 0.2	0.9 ± 0.6	0.38
ΔTotal fat (kg)	-1.4 ± 0.8	0.8 ± 1.0	0.09	-0.2 ± 0.7	-0.1 ± 1.0	0.96
ΔAbdominal fat (g)	-38 ± 58	275 ± 60	<0.0001	117 ± 52	180 ± 99	0.64

Data are mean ± SEM.

Table 3. Risk of incident glucose disorders at mean follow-up of 11.8 years.

	Incident glucose disorders			Incident diabetes mellitus		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Base model						
Age	1.06	1.02–1.10	0.006	1.09	1.01–1.18	0.029
BMI	0.98	0.86–1.12	0.78	0.94	0.72–1.23	0.66
Known HIV infection	0.96	0.89–1.04	0.33	0.95	0.82–1.11	0.52
AIDS-defining illness	1.79	0.97–3.28	0.061	2.31	0.73–7.54	0.15
Multivariate analyses [a]						
Metabolic parameters						
Baseline fasting glucose	2.67	1.70–4.20	<0.0001	5.11	1.92–13.63	0.001
Baseline 2-h glucose	1.47	1.29–1.68	<0.0001	5.14	2.17–12.17	<0.0001
Baseline triglycerides	1.03	0.96–1.09	0.43	1.01	0.85–1.18	0.95
Baseline HDL	0.67	0.28–1.63	0.38	0.35	0.05–2.40	0.28
Baseline C-peptide	1.33	1.04–1.70	0.026	1.71	1.04–2.85	0.036
Baseline fasting insulin	1.02	0.97–1.08	0.37	1.08	0.99–1.17	0.10
Insulin resistance	1.09	0.88–1.35	0.42	1.28	0.89–1.85	0.19
Lipodystrophy presence	1.08	0.41–2.82	0.88	1.02	0.09–15.13	0.99
Body composition parameters[b]						
Early abdominal fat gain	2.65	1.02–6.85	0.04		–	
Medium-term abdominal fat gain	3.16	1.30–7.68	0.01		–	
Medication exposures						
Nucleoside reverse transcriptase inhibitor class						
Stavudine	0.62	0.34–1.14	0.312	0.45	0.14–1.45	0.318
Zidovudine	0.84	0.44–1.60	0.59	0.87	0.24–3.17	0.83
Didanosine	0.81	0.45–1.45	0.47	0.63	0.20–2.12	0.46
Protease inhibitor class						
Saquinavir	0.70	0.39–1.26	0.23	1.01	0.32–3.16	0.99
Ritonavir	0.92	0.49–1.73	0.79	0.91	0.26–3.12	0.87
Indinavir	1.38	0.69–2.77	0.36	1.12	0.31–4.02	0.87
Nelfinavir	0.55	0.28–1.10	0.09	0.09	0.01–0.78	0.028
NNRTI class	1.10	0.49–2.46	0.83	0.39	0.09–1.48	0.16

HDL, high density lipoprotein cholesterol; NNRTI, nonnucleoside reverse transcriptase inhibitors.
[a]In Cox regression analyses, each parameter was added singly to a base model containing age, BMI, known HIV duration and AIDS at baseline.
[b]Cox regression analyses that entered change in abdominal fat included the covariates the base model (age, BMI, known HIV duration and AIDS at baseline) and the metabolic parameters of baseline fasting glucose and C-peptide.

glucose and C-peptide as covariates (Table 3). Early abdominal fat gain was associated with a significantly increased independent risk of incident glucose disorders (hazard ratio 2.65, 95% CI 1.02–6.85, $P = 0.04$). In this model, only baseline C-peptide was also independently associated with a higher risk of incident glucose disorders (hazard ratio 1.61, 95% CI 1.07–2.44, $P = 0.02$).

In a model that contained medium-term abdominal fat gain and age, AIDS, glucose and C-peptide as covariates, medium-term abdominal fat gain was also significantly associated with increased risk of incident glucose disorders (hazard ratio 3.16, 95% CI 1.30–7.68, $P = 0.01$; Table 3). Similarly, baseline C-peptide was also independently associated with a higher risk of incident glucose disorders (hazard ratio 1.44, 95% CI 1.01–2.04, $P = 0.04$).

Associations were sought between longitudinal changes in abdominal fat and incident diabetes in separate Cox regression analyses. A nonsignificant trend was found between medium-term abdominal fat gain and incident diabetes (hazard ratio 8.75, 95% CI 0.72–105.83, $P = 0.09$).

Ever-exposure to antiretroviral medication and risk of incident glucose disorders were examined using Cox regression analyses (Table 3). The base model included age, BMI, known HIV-infection duration and past AIDS-defining illness as covariates. To the base model, ever-exposure to each of the individual medications was added. No associations were found for risk of incident glucose disorders and individual medication exposures. Similarly, no association was found between individual medication exposures and incident diabetes, with the exception of nelfinavir exposure, which showed a risk reduction.

Discussion

In this longitudinal cohort study, high rates of incident glucose disorders were found in men with longstanding treated HIV infection. To our knowledge, this is the longest duration of follow-up for incident glucose disorders in treated HIV infection. The rate of glucose disorders was 34.5/1000 PYFU; prediabetes 24.3/1000 PYFU and diabetes 10.2/1000 PYFU. Abdominal fat gain and traditional risk factors of age and fasting and 2-h

glucose were associated with incident glucose disorders in the long-term.

Prior studies have consistently shown increased diabetes risk in treated HIV infection [7–10,16–19]. The incidence rate in our cohort was similar to cohorts in France and Taiwan (14.1 [9] and 13.1 [19] per 1000 PYFU, respectively), but exceeds that found in D:A:D (5.72/1000 PYFU) [8], the Swiss cohort (4.4/1000 PYFU over 4.3 years) [10] and a recent Thai study (5.0/1000 PYFU, mostly female patients over 7 years) [11]. Higher incidence rates have been reported in the United States Women's Interagency HIV Study (17.0–25.0/1000 PYFU) [7,17], an Italian cohort (20.6/1000 PYFU) [18], and the United States Multicenter AIDS Cohort Study (47/1000 PYFU) [16]. Notable differences between study cohorts may explain these differences, including sex, age, obesity, HIV duration and diabetes ascertainment methodology.

In the current study, a subgroup representative of the cohort underwent additional screening with a follow-up OGTT. Strikingly high rates of glucose disorders were detected: 60% of the subgroup had IGT or diabetes. In those with normal fasting glucose, the OGTT found IGT in 45% and diabetes in 10%, detecting approximately twice the rate of glucose disorders as fasting glucose alone. Performance of OGTT screening likely accounted for the steep rises in incident glucose disorders observed in the Kaplan–Meier curves (Fig. 2). As the glycosylated haemoglobin measure has been shown to under diagnose glucose disorders [20] and under estimate glucose control in treated HIV infection [21], our findings suggest that the OGTT should be considered best practice for accurate ascertainment of glucose status in treated HIV infection.

As for the general population, the current study found that traditional risk factors held the strongest associations with incident glucose disorders, namely increasing abdominal adiposity, age and elevated C-peptide, rather than HIV-infection specific risk factors. Older age at baseline was a significant determinant of increase of incident glucose disorders and diabetes, consistent with prior studies in people with treated HIV infection [9,10]. Abdominal fat gain was also a strong independent predictor of incident glucose disorders in this cohort. Few studies have examined longitudinal weight gain and risk of incident diabetes in treated HIV infection. To our knowledge, this is the first study to report that early-term and medium-term gains in abdominal fat (measured directly by DEXA) are associated with increased risk of incident glucose disorders. In those who gained abdominal fat over 12 months and 2–4 years observation, we found a two-fold to three-fold increased risk of incident glucose disorders at long-term follow-up, independent of covariates. Importantly, the majority of participants were in the healthy BMI range and none were obese. Further, the mean difference in abdominal fat gain in participants who developed glucose disorders was modest (230–320 g), suggesting that predominantly healthy-weight men with treated HIV infection may be at greater susceptibility to diabetes with modest abdominal fat gain. Other studies have also shown the importance of weight on risk of incident diabetes. D:A:D recently reported the impact of early BMI gain and incident diabetes risk in treated HIV infection: the highest quartile of BMI gain 1 year after cART initiation was associated with a 2.6-fold increase in incident diabetes, observed within each weight category of underweight, healthy, overweight or obese [22]. No risk increase was observed for lesser BMI gains [22], which might be explained as BMI is an imprecise estimate of adiposity and provides no estimate of abdominal obesity. Early D:A:D analyses also demonstrated that baseline overweight or obese BMI was associated with two-fold and four-fold increased incident diabetes risk, respectively, compared with healthy range BMI [8]. Further, a 10-year French observational study of diabetes incidence found that abdominal obesity was a stronger correlate of incident diabetes than BMI in treated HIV infection, with a 3.9 hazard ratio for elevated waist–hip ratio, compared with overweight and obese BMI (hazard ratio 1.9 and 2.9, respectively [9]). Thus, abdominal fat and weight gain in treated HIV infection are important clinical parameters identifying future diabetes risk, that can be addressed early with lifestyle intervention.

Baseline metabolic predictors of incident glucose disorders included higher fasting C-peptide levels and 2-h postchallenge glucose levels. In multivariate Cox regression analyses, baseline C-peptide levels were consistently independently associated with incident glucose disorders, even in analyses that included abdominal fat gain. Fasting C-peptide levels is commonly used to assess endogenous insulin secretion, in preference to fasting insulin. Fasting C-peptide levels more accurately reflecting portal insulin secretion in contrast to fasting insulin levels, which show high intra-individual variability, are subject to extensive first-pass hepatic clearance and variable peripheral clearance. Whilst the parameters of abdominal obesity and OGTT responses may be primary in identifying those at risk of glucose disorders in the clinical setting, C-peptide levels may be useful in research settings in understanding the progression of beta-cell decline to overt diabetes in treated HIV infection.

The baseline 2-h OGTT response was also associated with long-term incident glucose disorders, noting that the mean response for those with incident glucose disorders was within the normal range. Whilst IGT and IFG both carry a higher risk for incident diabetes and incident atherosclerotic cardiovascular disease in the general population [23], cardiovascular mortality in IGT appears closer to that of diabetes and much greater than that

observed in IFG [24–28]. Studies in general populations have shown that a high-end normal range 2-h glucose response appears to be a harbinger of future adverse health events, as shown in a meta-analysis of 20 studies of mean follow-up 12.4 years [29]. Given the strikingly high IGT detection rate in our cohort whenever the screening OGTT was utilized and the established associations of IGT and cardiovascular risk, the OGTT may be the optimal test for early identification of both diabetes and cardiovascular risk in treated HIV infection.

Of the HIV-specific factors examined, only longer known HIV-infection duration at follow-up was associated with increased incident diabetes. Cohort participants with and without incident glucose disorders had similar cART exposure durations. Nelfinavir appeared to be associated with reduced incident diabetes risk in multivariate models; this result might be explained by prescription bias: many protease inhibitors available at that time were identified to increase insulin resistance and nelfinavir may have been preferentially prescribed. Overall, no increased risk of diabetes was observed with specific exposure to stavudine, zidovudine or didanosine, in contrast to other studies [7,8,17], which may be because of cohort differences in age, sex, size and cART era. Prior studies have shown relationships between medication exposure and incident diabetes. D:A:D reported that cumulative cART exposure independently increased incident diabetes relative risk by 11% [8]. Stavudine exposure was associated with a 19% incident diabetes relative risk increase, with lesser risk observed with zidovudine and didanosine; in contrast, ritonavir and nevirapine appeared protective [8]. Cohort data examination over the longer term with appropriate diabetes ascertainment will assist in clarifying any relationships between cART exposure and glucose disorders.

Strengths of this study include the long duration of follow-up and the comprehensive baseline evaluation including detailed metabolic measures and longitudinal measures of abdominal adiposity using DEXA in a subgroup and OGTT screening at 10–12 years into the observation, again in a representative subgroup. Limitations include relatively small numbers potentially underpowering some analyses. The cohort was male and all had received long-term cART; whilst representative of treated HIV infection in Australia, our results cannot be extrapolated to untreated HIV infection, women, children or resource-poor settings. Analyses on risk of exposure from medications were very limited, as data on duration of exposure to different medications were not available. Approximately 25% of the original cohort did not attend follow-up beyond 2 years; drop-outs may have biased the rates of glucose disorders ascertained. Whilst analyses found that drop-outs were mostly similar to those in long-term follow-up (as were those with 2–10 vs. 10–18 years follow-up) survivor bias may be still have been present. DEXA measures of adiposity were limited to 4 years, therefore, our study does not allow elaboration of longer term changes in central adiposity and diabetes risk. Repeat OGTTs at 10–12 years follow-up were performed in a subgroup only; again, whilst representative of the cohort, this may have biased the incidence and type of glucose disorders detected. Data on co-infection with hepatitis C virus were not available and did not allow for evaluation of this risk factor, which also increases insulin resistance and diabetes risk. Given the setting and long duration of follow-up, many in the cohort were exposed to long duration cART and many to older antiretroviral medications. This prevents our results being extrapolated to populations exposed only to more modern cART medications. Medium-term and long-term data are lacking for more modern antiretrovirals and are urgently needed.

Medication prescription bias may have existed, as medications with apparently lower diabetes-risk became standard of care during the observation period.

Conclusion

In this population, treated HIV infection was associated with high rates of incident glucose disorders in the long-term, with strikingly high rates detected by OGTT screening. Modest abdominal fat gain, even in the healthy weight range, was associated with a two-fold to three-fold increased risk of incident glucose disorders. Accurate determination of glucose status in treated HIV infection will identify individuals for early intervention with preventive weight management strategies for cardiometabolic health maintenance and diabetes prevention.

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Conflicts of interest

There are no conflicts of interest.

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