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The concomitant use of second-generation antipsychotics and long-term antiretroviral therapy may be associated with increased cardiovascular risk

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ABSTRACT

To study the effect of concurrent use of second-generation antipsychotics (SGAs) on metabolic syndrome (MetS) components conferring increased cardiovascular risk in a sample of human immunodeficiency virus (HIV)-infected adults taking antiretroviral therapy (ART). A retrospective study of participants consecutively recruited at the UCSD HIV Neurobehavioral Research Program examined effects of combined ART and SGAs on body mass index (BMI), nonfasting serum lipids, diabetes mellitus (DM) incidence, and mean arterial pressure (MAP). Metabolic outcome variables and covariates were compared using *t*-tests, Chi-squared or Fisher's exact tests. Linear and logistic multivariable models explored metabolic outcomes for participants taking (SGA+) or not taking (SGA−) concomitant SGAs, after controlling for demographic and HIV disease- and ART-related covariates. Of 2229 HIV-infected participants, 12% (N=258) were treated with SGAs. In multivariable models adjusted for relevant covariates, the SGA+ group had significantly higher mean triglycerides, significantly higher odds of DM, significantly higher MAPs and marginally higher BMI. The use of SGAs in HIV-infected adults taking ART was independently associated with worse indicators of MetS and cardiovascular risk. Aggressive monitoring for the metabolic complications from concurrent SGA and ART is indicated in all patients receiving these medication combinations.

1. Introduction

Psychiatric disorders are more prevalent in human immunodeficiency virus (HIV) infected people than in the general population (Atkinson et al., 1988, 2008; Bing et al., 2001; Cournos and McKinnon, 1997; Gaynes et al., 2008; Rabkin, 2008). Prevalence of HIV infection among persons with serious mental illness (SMI) is estimated to be between 3% and 23%, or more than 10-fold higher than the 0.4% in the general United States population (Cournos and McKinnon, 1997; Lee et al., 2011; Meyer, 2003). Due to the high SMI prevalence in this population, psychotropic medications are commonly used by HIV-infected patients (Bing et al., 2001; Gaynes et al., 2008; Thompson et al., 2006; Vitiello et al., 2003; Walkup et al., 2004). Data from the US Medicaid population obtained from July 2002 through June 2003 showed that 89% of the HIV-infected people with SMI used psychotropic medications (Lee et al., 2011).

Antipsychotics are commonly employed for patients with SMI, in part due to the broad array of FDA-approved indications for antipsychotics in adults, including the acute and maintenance treatment of schizophrenia, acute mania, maintenance treatment in bipolar disorder and adjunctive therapy for major depressive disorder (MDD) (Meyer, 2010). While both the older "typical" and newer "atypical" medications (second-generation antipsychotics or SGAs) are widely used, SGAs have a therapeutic advantage due to a lower incidence of extrapyramidal symptoms (Meyer, 2010). Though SGA use has steadily increased due to this improved neurological tolerability and the availability of multiple generic drugs in this class, the enthusiasm for certain SGAs has been tempered by their association with metabolic abnormalities (e.g. hyperglycemia, weight gain, and hyperlipidemia) (Stahl et al., 2009) and an increased prevalence of metabolic syndrome (MetS)

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(Meyer and Stahl, 2009). MetS is a constellation of frequently concurrent conditions, including central obesity, atherogenic dyslipidemia, hypertension, glucose intolerance/diabetes mellitus (DM) and a prothrombotic/inflammatory state, that increase the risk of cardiovascular and cerebrovascular diseases (Girman et al., 2005; Wannamethee et al., 2005). Greater numbers of MetS components predict higher risk for myocardial infarction and stroke (Girman et al., 2005; Wannamethee et al., 2005). Whether due to treatment or inherent biological factors associated with SMI, MetS prevalence is 2–3 times greater in persons with schizophrenia or bipolar disorder compared to the general population (McEvoy et al., 2005), and thus represents an important source of increased cardiovascular risk.

In addition to possible biological variables related to the diagnosis of SMI itself, SMI patients also have a higher prevalence of behavioral factors (smoking tobacco, poor dietary habits, and inactivity) that amplify the risk of cardiovascular mortality compared to age-matched peers without SMI (Meyer, 2010), and higher rates of medical comorbidity noted at the time of diagnosis before exposure to antipsychotics (Meyer, 2010). Subsequent exposure to SGAs may therefore increase the risk of cardiovascular mortality for SMI patients as suggested by the increasing relative risk of cardiovascular mortality in SMI patients during the SGA era (Colton and Manderscheid, 2006; De Hert et al., 2009; Saha et al., 2007).

The development of metabolic adverse effects is not unique to SGAs, with an extensive literature documenting the impact of combination antiretroviral therapy (cART) for HIV on lipids, weight and cardiovascular risk. While cART markedly reduces mortality due to HIV infection, it is also associated specifically with increased prevalence of MetS (25–96%) (Carr, 2003; Falutz, 2007; Feeney and Mallon, 2011; Germinario, 2003). Despite the high rates of HIV and psychiatric comorbidity, and the known metabolic effects of SGAs and antiretrovirals, the metabolic consequences of SGA exposure in HIV-infected individuals have received virtually no coverage in the literature (Singh and Goodkin, 2007). This study attempts to address the gap in the clinical understanding of the metabolic impact of SGA use in HIV patients.

2. Methods

2.1. Study design

This retrospective, cross-sectional study examined metabolic outcomes in 2229 antiretroviral-treated, HIV-infected adults.

2.2. Subjects

Participants were HIV-infected volunteers consecutively recruited for clinical studies at the UCSD HIV Neurobehavioral Research Program (HNRP) in San Diego, CA, between January 1995 and September 2011. Participants were enrolled in various studies sponsored by the National Institute of Mental Health and the National Institute on Drug Abuse including 1097 from "The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER)" Study, 255 from "The California NeuroAIDS Tissue Network (CNTN)", 195 from "NeuroAIDS: Effects of Methamphetamine and Hepatitis C Virus", 179 from "Prospective Memory and HIV Infection (PROM)" and 509 from smaller HNRP studies.

Inclusion criteria were serologically documented HIV infection, age $\geq$ 18 years, current treatment with antiretroviral therapy (ART) and adequate documentation of concomitant medication use. Because the HNRP studies HIV-associated neurocognitive disorders, volunteers with conditions that prevented individuals from undergoing detailed neuropsychological testing (e.g., acute psychosis) or might confound assessment of specific HIV-related brain disorders were excluded (e.g., type I DM and schizophrenia, since the former can be associated with mircrovascular disease of the brain and neurocognitive impairment, and schizophrenia is a neurodevelopmental disorder with deficits in executive function, among other impairments). All subjects completed structured medical, psychiatric, and laboratory assessments. The duration of treatment with ARTs and SGAs was collected through standardized case report forms by trained research nurses. For the purpose of this study we selected data from the participant's most recent visit.

Protocols were approved by the Institutional Review Boards of participating institutions. Written informed consent was obtained from all study participants before enrollment.

2.3. Clinical evaluation and laboratory measures

Standardized general medical histories and physical examinations were performed, and blood pressure measurements obtained using automated calibrated mercury sphygmomanometers with appropriate cuff sizes. Systolic (SBP) and diastolic (DBP) measures were obtained from seated subjects to calculate mean arterial pressure (MAP). Height and weight for calculating body mass index (BMI) were measured. A diagnosis of DM was ascertained according to Expert Committee on the Classification of Diabetes Mellitus (2003) (Genuth et al., 2003). Venipuncture for nonfasting laboratory studies was performed at the time of the visit. After clotting, serum was assayed for total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum triglycerides (TG) and glucose. TC was dichotomized as high ($>$ 200 mg/dL) or normal, HDL-cholesterol values as low ($<$ 40 mg/dL) or normal; the ratio of TC/HDL-cholesterol was also calculated (TC/HDL). Hepatitis C virus (HCV) serology (HCV Antibody essay: LabCorp, Burlington, NC) was examined because of the association of chronic HCV infection with DM (Mehta et al., 2000), insulin resistance (Romero-Gomez, 2006), impaired lipid metabolism (Lonardo et al., 2004; Negro and Sanyal, 2009) and MetS (Grigorescu et al., 2008).

2.4. Characterization of HIV infection

A detailed history of HIV illness and treatment was captured by a combination of questionnaires and standardized interview. Nadir CD4 cell count since HIV infection was self-reported. Past and current antiretroviral usage including usage dates, dose, and schedule for each drug was captured by self-report standardized questionnaires that were reviewed with clinicians. ART exposure was categorized as current use, past use, or never used. ART regimens were dichotomized as (1) protease inhibitor (PI) based vs. non-PI based (Nolan, 2003); and (2) Efavirenz (EFV) based vs. non-EFV based (Haubrich et al., 2009). Blood CD4 cell counts were measured by flow cytometry. HIV RNA levels were quantified in plasma and cerebrospinal fluid (CSF) by reverse transcriptase-polymerase chain reaction (Amplicor®, Roche Diagnostic Systems, Indianapolis, IN) using an ultrasensitive assay (lower quantification limit $<$ 50 copies/mL).

2.5. Psychiatric diagnoses and prescribed SGAs

Depending on the specific protocols, psychiatric diagnoses were assessed using either the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988), the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al., 1996), or the Structured Clinical Interview for DSM-IV criteria (SCID IV) (Spitzer et al., 1992). Each of these assessments included modules for diagnosis of mood disorder, alcohol use disorders, and non-alcohol substance use disorders using DSM-IV criteria. Participants in the antipsychotic exposed group (SGA+) reported current use of one or more of the following SGAs: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone.

2.6. Statistical analysis

Two groups (SGA− and SGA+) were compared on demographic, HIV-associated, and psychiatric characteristics, using a two-sample t-test and Chi-square test for continuous and categorical variables, respectively. Two sample t-tests and Chi-square tests were also performed to analyze the effect of SGA use on eight metabolic variables: BMI, MAP, TC, HDL cholesterol, LDL cholesterol, TC/HDL ratio, triglycerides and DM. Additionally, TC and TG values were also analyzed on a dichotomized scale based on the most recent guidelines for risk ranges: TC $\geq$ 200 mg/dL, HDL $<$ 40 mg/dL, LDL $\geq$ 130 mg/dL, TC/HDL $\geq$ 5, and TG $\geq$ 150 mg/dL (Blackburn et al., 2008; Lemieux et al., 2000; Mannucci et al., 2008). Since each metabolic outcome was analyzed separately, we used all data available for each outcome to maximize the power of each analysis. Thus, sample sizes for regressions varied for each variable. HIV RNA levels were $\log_{10}$ transformed and analyzed both continuously and categorically, as undetectable vs. detectable.

Effects of individual SGAs on the metabolic outcomes were evaluated in a series of univariable analyses using the methods described above. In addition, outcomes were tested for an association with treatment duration of each SGA using Spearman correlation or logistic regression.

The use of individual ART medications in the SGA+ group was compared to that in SGA− group using the Chi-square test (or Fisher's exact test, if appropriate). The effects of PIs with known metabolic risks on the metabolic outcomes in this study were evaluated with t-tests (or Wilcoxon rank-sum test) and Chi-square test (or Fisher's exact test).

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Multivariable analysis was performed for every metabolic outcome to control for the effects of covariates. Linear and logistic regressions were used to analyze continuous and categorical outcomes, respectively. Power transformations were applied to selected outcomes to achieve normally distributed residuals. The following 16 covariates were tested for association with each outcome in a series of univariable regressions: age, sex, ethnicity, HCV co-infection, estimated duration of HIV infection, CD4 nadir, current CD4, detectable plasma viral load (VL), duration of current ART regimen, PI-based regimen, EFV use, current MDD and lifetime alcohol and other substance dependence diagnoses. Each multivariable model initially included a SGA group indicator (SGA+/SGA−) and those covariates that showed an association with an outcome at 0.20 significance level (Vittinghoff et al., 2005). Model selection processes, using Akaike Information Criterion (AIC), were applied to reduce each model to include only the SGA group indicator and covariates significant at the $P=0.10$ level. Effect sizes (ESs) and their 95% confidence intervals were calculated for each univariable (unadjusted) and multivariable model predicting a metabolic outcome. In linear regressions, the ES was measured as difference in means standardized by residual standard deviation (Cohen's *d*). Odds ratios (OR) were used to quantify the ES for logistic regressions.

The analyses were carried out using the statistical software R version 2.10.0 (www.r-project.org). All tests were two-sided and used a significance level of 0.05, except where specified otherwise.

3. Results

Demographic, anthropometric and metabolic variables for 2229 HIV-infected individuals, categorized according to their current use of SGAs, are presented in Table 1. The sample was predominantly white (47%) and male (81% of total sample), with a mean age of 45 years. The SGA+ group ($N=258$) comprised 12% of the total sample and included higher proportions of women (25% vs. 18%) and African-Americans (40% vs. 31%) than the SGA− group.

Most participants had longstanding HIV infection and low nadir CD4 counts (median 117 cells/mm^3). They had taken their current antiretroviral regimen for over 1 year, with good virologic control and immune reconstitution based on high current CD4 counts (median 436 cells/mm^3). The SGA+ and SGA− groups did not differ significantly in current and nadir CD4 cell counts, plasma VLs or duration or composition of current ART regimen. About two-thirds were on a PI-based regimen, which in the majority of cases was boosted with ritonavir (RTV) (54% of SGA− and 59% of SGA+); EFV-based regimens were less common in the SGA+ group compared to SGA− (see Supplemental Table). The two SGA groups did not differ in use of specific antiretrovirals known for causing more pronounced metabolic side effects (stavudine [D4T], RTV, zidovudine [ZDV], and indinavir [IDV]; Grunfeld and Feingold, 1992).

In univariate analyses, subjects in the SGA+ group had higher BMI (27.3 vs. 26.2; $t=2.9$; $P=0.004$) and a higher proportion of obese subjects (27% vs. 18%; $\chi^2=10.9$, $df=1$, $P=0.001$). SGA+ subjects also were more likely than SGA− to have DM (15% vs. 9%; $\chi^2=5.0$, $df=1$, $P=0.025$). SGA+ and SGA− subjects exhibited no significant differences in mean lipid fractions (TC, HDL, LDL, and TG), or mean arterial blood pressure.

Numerous variables explained a part of the variance in the metabolic outcomes including age, gender, ethnicity, HCV status, CD4 counts, type of ART, and specific psychiatric comorbidities such as lifetime substance dependence diagnosis. Table 3 shows the results of multivariate analyses adjusting for demographic and disease covariates. SGA+ participants had significantly higher MAP (ES=0.28, 95% CI=0.08–0.49, $P=0.006$), TG (ES=0.28, 95% CI=0.06–0.50, $P=0.014$) and diabetes prevalence (OR=2.28, 95% CI=1.29–4.02, $P=0.004$) than SGA− subjects. In addition, SGA+ participants had non-significantly higher BMI (ES=0.16, 95% CI=−0.01–0.33, $P=0.068$). When exposure to antiretrovirals known to be associated with metabolic side effects (RTV, d4T, ZVD, and IDV) was added to the models, the results of multivariable analyses did not differ significantly from those reported in Table 3. The two groups had similar TC and lipid subfractions (data not shown).

Of the 258 SGA+ participants the vast majority (> 90%) were prescribed only one SGA. The most commonly prescribed SGA was quetiapine (57%), followed by risperidone (25%), olanzapine (24%), aripiprazole (14%), ziprasidone (6%), clozapine (1%) and paliperidone (1%). The median exposure of the current SGA regimen was 15 months.

Secondary analyses examined differences between individual SGA exposure and metabolic variables. Compared to the SGA− group,

Table 1
Demographic and clinical characteristics of 2229 HIV-infected participants on cART.

Sample characteristics	SGA− (*n*=1971)	SGA+ (*n*=258)	*p*-Value
Demographics			
Age (years)[a]	45.5 (9.4)	45.3 (8.0)	ns
Gender (male)[b]	1613 (82%)	194 (75%)	0.013*
Ethnicity[b]			
Black	619 (31%)	103 (40%)	0.007*
Hispanic	350 (18%)	32 (12%)	0.040*
White	936 (47%)	114 (44%)	ns
Others	66 (3%)	9 (4%)	ns
Clinical			
HIV disease status			
Estimated duration of HIV infection (months)[a]	146 (82)	148 (86)	ns
Nadir CD4 (cells/mm^3)[c]	113 (26–232)	147 (40–226)	ns
Current CD4 (cells/mm^3)[c]	439 (258–644.5)	425 (258–615)	ns
Current plasma VL ($\log_{10}$ c/mL)[c]	1.7 (1.7–2.4)	1.7 (1.7–2.6)	ns
Antiretroviral therapy			
Duration of current regimen (months)[c]	15.2 (5.4–34.3)	16.3 (6.9–31.8)	ns
PI-based (%)[b]	1233 (63%)	170 (66%)	ns
EFV-based (%)[b]	507 (26%)	46 (18%)	0.007*
Hepatitis C virus status (% positive)[b]	281 (14%)	47 (18%)	ns

All percentages based on the complete (non-missing) data only. *Age*: *N* (%) missing: 0; *gender N* (%) missing: 0; *ethnicity N* (%) missing: 0; *est. duration HIV infection*, *N* (%) unknown: 117 (5.2%); *Nadir CD4*, *N* (%) missing: 230 (10.3%); *current CD4*, *N* (%) missing: 45 (2%); *current plasma VL*, *N* (%) missing: 213 (9.6%); *duration of current ART regimen*, *N* (%) missing: 106 (4.8%); *diagnosis of diabetes mellitus*, *N* (%) missing: 316 (14.2%); *BMI*, *N* (%) missing: 101 (4.5%); *HCV* serostatus, *N* (%) missing: 0.

* *p*-Value from the Chi-square test.
[a] Mean (standard deviation).
[b] Number (%).
[c] Median (inter-quartile range).

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Table 2
Psychiatric diagnoses and exposures to SGAs.

Psychiatric variables	SGA− (*n*=1971)	SGA+ (n=258)	*p*-Value
Psychiatric diagnosis			
Current substance abuse/dependence[a,b]	97 (5%)	17 (7%)	ns
Lifetime substance abuse/dependence[a,b]	1265 (69%)	186 (78%)	0.011*
Alcohol abuse/dependence[a,b]	944 (52%)	141 (59%)	0.047*
Current major depressive disorder (MDD)[a,b]	198 (11%)	51 (22%)	<0.001*
Bipolar disorder[a,b]	53 (24%)	47 (57%)	<0.001*
SGA use			
Daily dose for most commonly used SGAs (mg)[c]		12.4 (9.6)	
Aripiprazole (*N*=14)			
Olanzapine (*N*=43)		14.2 (11.9)	
Quetiapine (*N*=81)		241 (276)	
Risperidone (*N*=29)		2.3 (1.6)	
Ziprasidone (*N*=6)		123 (144)	
Duration of current treatment (months)[d]		15.9 (5–36.3)	

* *p*-Value from the Chi-square test.
[a] Number (%).
[b] Percentages based on non-missing data only. Current substance abuse/dependence: *N* (%) missing 231(10%); lifetime substance abuse/dependence: *N* (%) missing 163 (7%); alcohol abuse/dep: *N* (%) missing 163 (7%); current major depressive disorder (MDD): *N* (%) missing 232 (10%); bipolar disorder: *N* (%) missing 1926 (86%).
[c] Mean (standard deviation), daily dose: *N* (%) missing 83 (32%).
[d] Median (inter-quartile range). Duration of current treatment: *N* (%) missing 14 (5%).

Table 3
Multivariable analyses of correlates of metabolic variables affected by second-generation antipsychotic drugs. All correlates presented in the table were included in the models of the effects of correlates on each metabolic variable. Effect size (ES) is expressed in Cohen's *d* for body mass index (BMI), mean arterial pressure (MAP), triglycerides (TG). ES is expressed as adjusted odds ratio for diabetes mellitus (DM). 95% confidence intervals are in parentheses. Sample sizes were for BMI, *N*=1527; MAP, *N*=1051; TG, *N*=985; DM, *N*=1051.

Metabolic variable	Correlate			
	BMI	**MAP**	**TG**[a]	**DM**
SGA	0.16* (−0.01, 0.33)	0.28*** (0.08, 0.49)	0.28** (0.06, 0.50)	2.28*** (1.29, 4.02)
Age[b]		0.11*** (0.04, 0.19)		1.62*** (1.30, 2.03)
Male	−0.45*** (−0.58, −0.32)	0.28*** (0.13, 0.44)	0.28*** (0.12, 0.44)	
Ethnicity[c]				
White	−0.08 (−0.20, 0.03)	−0.26*** (−0.40, −0.12)	0.36*** (0.22, 0.51)	
Hispanic	0.05 (−0.11, 0.21)	−0.36*** (−0.55, −0.18)	0.50*** (0.31, 0.69)	
Other	−0.42** (−0.73, −0.11)	−0.40** (−0.73, −0.06)	0.22 (−0.15, 0.60)	
Hepatitis C virus status				1.97** (1.23, 2.15)
Estimated HIV duration (years)[d]		0.05** (0, 0.10)		
CD4 Nadir[d]			−0.05* (−0.1, 0)	
CD4[e]	0.04*** (0.02, 0.05)		0.04*** (0.02, 0.06)	1.06* (1.00, 1.13)
Detectable plasma viral load				
Protease inhibitor-based regimen	−0.10* (−0.21, 0)	−0.18*** (−0.31,−0.06)	0.19*** (0.06, 0.32)	
Lifetime substance dependence diagnosis	−0.11* (−0.22, 0)			

* $p < 0.10$.
** $p < 0.05$.
*** $p < 0.01$.
[a] TG values were log transformed.
[b] ES per 10 years increase.
[c] Reference group is black.
[d] ES per 5 year increase.
[e] ES per 100 cell count increase.

quetiapine users showed significantly greater BMI (27.4 vs. 26.2 kg/m^2, $t=-2.03$, $P=0.044$) and a higher proportion of DM (17% vs. 9%, $\chi^2=5.42$, $df=1$, $P=0.02$). Odds of TC/HDL ratio > 5 increase with longer exposure to quetiapine (OR=1.27, 95% CI=1.06–1.53, $P=0.009$). Compared to the SGA− group, risperidone users had significantly higher cholesterol levels (196.7 vs. 182.6 mg/dL, $t=-2.02$, $P=0.044$) and proportion of people with TC level ≥ ≥200 mg/dL (48% vs. 31%, $\chi^2=4.83$, $df=1$, $P=0.028$). However, among those on risperidone, longer exposure to the drug was associated with lower TC levels ($r=-0.33$, $P=0.037$), lower odds of HDL< <40 mg/dL (OR=0.71, 95% CI=0.52–0.98, $P=0.035$), lower TC/HDL ratio ($r=-0.41$, $P=0.026$), lower odds of TC/HDL ratio ≥ 5 (OR=0.77, 95% CI=0.57–1.04, $P=0.084$), lower LDL ($r=-0.46$, $P=0.017$), and higher odds of diabetes (OR=1.96, 95% CI=1.03–3.74, $P=0.042$). Individuals taking aripiprazole had higher BMI (28.3 vs. 26.2 kg/m^2, Wilcoxon $W=19{,}019$, $P=0.024$) than those not prescribed a SGA. Those on olanzapine had a larger proportion with triglycerides ≥ 150 mg/dL compared to the SGA− group but this difference was not statistically significant (71% vs. 56%, $\chi^2=2.84$, $df=1$, $P=0.092$).

Analysis of ART effects on metabolic outcomes showed that RTV was associated with significantly lower mean DBP (75.8 vs. 77.6 mm Hg, $t=3.68$, $P<0.001$) and lower MAP (92.6 vs. 93.9 mm Hg, $t=2.57$, $P=0.01$), lower mean (sqrt) HDL cholesterol (6.65 vs. 6.84 mg/dL, $t=2.92$, $P=0.004$), higher proportion of people with HDL < 40 (44% vs. 38%, $\chi^2=7.34$, $df=1$, $P=0.007$), higher mean (log10) TC/HDL ratio (0.62 vs. 0.6, $t=-2.22$, $P=0.027$), higher

proportion of people with TC/HDL ≥ 5 (32% vs. 27%, $\chi^2=4.96$, $df=1$, $P=0.026$), higher mean ($\log_{10}$) triglycerides (2.25 vs. 2.19, $t=-4.64$ $P<0.001$), and higher proportion of people with triglycerides ≥ 150 mg/dL (60% vs. 53%, $\chi^2=11.39$, $df=1$, $P<0.001$).

Among the other ARTs, d4T use was associated with significantly higher mean DBP (79.6 vs. 76.5 mm Hg, $t=-2.82$, $P=0.005$), and marginally higher mean MAP (95.2 vs. 93.1 mm Hg, $t=-1.78$, $P=0.075$), while ZDV was associated with significantly lower average SBP (124.5 vs. 126.6 mm Hg, $t=2.42$, $P=0.016$), higher mean ($\log_{10}$) triglycerides (2.25 vs. 2.22, $t=-2.34$, $P=0.019$), higher proportion of people with triglycerides ≥ 150 mg/dL (62% vs. 55%, $\chi^2=4.58$, $df=1$, $P=0.032$), and higher proportion of diabetes (14% vs. 9%, $\chi^2=5.70$, $df=1$, $P=0.017$). IDV use was also strongly associated with diabetes (54% vs. 10%, Fisher's exact $P<0.001$).

A diagnostic psychiatric examination was conducted in > > 93% of the total sample, the results of which showed high prevalence of lifetime substance use disorders (65%) and current MDD (11%). As shown in Table 2, more SGA+ than SGA− participants had lifetime psychiatric diagnosis of substance use disorders (abuse or dependence; $\chi^2=6.47$, $df=1$, $P=0.011$) or alcohol use disorders (abuse or dependence; $\chi^2=3.95$, $df=1$, $P=0.047$), current MDD ($\chi^2=20.8$, $df=1$, $P<0.001$) and bipolar disorder ($\chi^2=28.6$, $df=1$, $P<0.001$).

HCV serostatus was associated with lower levels of TC (ES = −0.50) and LDL (ES = −0.58) (models not shown).

4. Discussion

This is the largest study to examine metabolic consequences of combining ART and SGA drugs in HIV-infected adults. Exposure to SGAs was independently associated with multiple components of the MetS including increased plasma triglycerides (TG), elevated BMI, higher MAP and increased prevalence of DM. These findings represent compelling evidence that the use of SGAs in HIV-infected individuals increases the risk of hyperlipidemia, hypertension and diabetes, as seen with the SGA use in HIV-*un*infected persons (De Hert et al., 2009). This effect was independent of the use of antiretroviral medications associated with metabolic side effects.

The concern about metabolic risk is not limited to the use of SGAs, as both HIV infection and ART are associated with metabolic abnormalities. Increased TG in untreated HIV infection may represent a consequence of the systemic inflammatory response to persistent HIV infection (Grunfeld and Feingold, 1992). Thus, some of the metabolic abnormalities may be attributable to neither ART nor SGAs. Nevertheless, the thymidine analog ART drugs are associated with dyslipidemia, insulin resistance and increased risk of DM (Carr, 2003; Ledergerber et al., 2007), as our analysis on ZDV and D4T confirms. Likewise, protease inhibitors have been linked to insulin resistance, dyslipidemia and central obesity possibly through increased mitochondrial oxidative stress (Penzak and Chuck, 2000). These atherogenic metabolic abnormalities probably contribute to the 26% increase in risk of heart disease for each year on cART (Friis-Moller et al., 2003).

Superimposed on this baseline level of metabolic risk in HIV patients, the use of SGAs is also known to be associated with an array of metabolic disturbances (Meyer, 2010). While data on quetiapine and risperidone in HIV-uninfected patients with schizophrenia show lower risk for weight gain, elevated triglycerides and hyperglycemia compared to olanzapine and clozapine, there is no substantial data on use in treated HIV patients. In our cohort, quetiapine was the most frequently prescribed psychotropic medication, consistent with previous reports (Freudenreich et al., 2010), and quetiapine users had a higher proportion of DM, underlining a possible additive effect of ART when combined with SGAs. Risperidone was the only SGA for which longer exposure was statistically associated with higher odds of having DM.

The combined effects of ART and psychotropic medications in increasing adverse metabolic outcomes can be explained by one of the several mechanisms, including competition for their metabolism by the same cytochrome P450 isoenzyme system (Singh and Goodkin, 2007) and direct biological effects at multiple loci. Many ARTs are potent inhibitors of cytochrome P450 enzymes, particularly CYP 3A4, and thereby increase serum concentrations of some antipsychotic drugs (e.g. quetiapine), leading to higher plasma antipsychotic levels and potentially more pronounced adverse effects (Singh and Goodkin, 2007; Thompson et al., 2006; Tseng and Foisy, 1999); however this pharmacokinetic interaction between ART and SGAs is not confirmed by the literature that does not correlate plasma level of SGAs to metabolic side effects (Coe and Hong, 2012; Suzuki et al., 2011). Both drug classes may decrease activity of the glucose transporter 4 in the myocyte cell membrane, leading to decreased glucose uptake, insulin resistance and hyperinsulinemia (Sathekge et al., 2010). Increased production of cytokines (Lihn et al., 2003; Pacenti et al., 2006) and mitochondrial toxicity in adipose tissue, both well-known side effects of ARTs, could induce adipocyte apoptosis (Buffet et al., 2005). Recent studies also have shown that chronic olanzapine treatment induces pro-inflammatory cytokine production, a risk factor for insulin resistance and cardiovascular disease (Victoriano et al., 2010). Both ARTs and SGAs disrupt adipogenesis in subcutaneous fat through alterations in the sterol regulatory enhancer-binding protein 1 (SREBP1) and peroxisome proliferator activated receptor gamma (PPAR-γ) resulting in elevated triglyceride and fatty acid levels which cause insulin resistance (Mallon et al., 2005; Dresner et al., 1999; Hadigan et al., 2003). Lastly, ARTs and SGAs are associated with increased levels of TNF-α, a pro-inflammatory protein, and leptin, a hormone that regulates appetite and weight (Vergara-Rodriguez et al., 2009). The finding that SGAs are associated with hypertension is consistent with mediation through weight gain or direct binding effects on alpha 2 receptors by olanzapine and risperidone (Abi-Dargham and Laruelle, 2005).

The decision to examine the concurrent use of SGAs and ARTs in our study population was driven by data showing that a high proportion of HIV-infected people have a past or current psychiatric diagnosis (Burnam et al., 2001). The proportion of HIV-infected adults taking SGAs in this cohort (11%) was higher than previously reported (4.7%) (Vitiello et al., 2003), and may relate to an evolution in psychiatric practice as SGAs are applied more broadly to conditions such as major depression.

The role of ART factors and HCV comorbidity was both examined. As expected, HCV status was associated with lower levels of TC and LDL (model not shown), a finding consistent with other reports that HCV co-infection in HIV-infected adults appears to reduce the risk of cART-associated dyslipidemia (Cooper et al., 2007). Psychiatric comorbidity may have influenced ART choice since EFV-based ART regimens were less common in the SGA+ group. Avoidance of EFV may possibly be based on clinicians' reluctance to prescribe EFV to patients with psychiatric disorders because of this drug's frequent neuropsychiatric side effects such as intense dreams, depression and anxiety (Himelhoch et al., 2007; Arendt et al., 2007). Regardless of the pattern of EFV use, the concomitant use of SGAs further increased metabolic risk as shown in the multivariable models.

This study has several limitations. We studied a sample of convenience, so the results may not be generalizable to the entire HIV-infected population. Because actively psychotic patients were excluded from most protocols comprising our sample, our participants may not be representative of all HIV-infected people taking antipsychotics (Lieberman et al., 2005). Although our HIV SGA+ cohort was more than twice as large as one previously

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described (Vitiello et al., 2003), the SGA+ cohort is still only 12% of the total sample (258 out of the 2229 total subjects). Larger SGA+ samples may provide different estimates of the comparative metabolic impact vs. an SGA− cohort. The absence of data on SGA dosing or plasma levels also omits an important aspect of SGA treatment that could influence metabolic risk. Our cross-sectional, observational design is vulnerable to biases including unmeasured confounders. Because of the retrospective nature of the study, baseline metabolic data was not available prior to ART or SGA use. Although fasting laboratory measurements were not obtained, recent large studies have demonstrated that, for some variables (e.g. triglycerides), nonfasting values may be more important than fasting levels in cardiovascular risk assessment (Eckel et al., 2010; Nordestgaard et al., 2007; Sarwar et al., 2010), and for other, lipid levels, there is relatively limited variability between the fasting and nonfasting states (Langsted et al., 2008). Moreover measurement of nonfasting lipid fractions may also ultimately better predict cardiovascular disease risk (Mora et al., 2008), as more representative of human usual metabolic conditions (Expert Committee on the Classification of Diabetes Mellitus, 2003).

When combined ART and SGAs are necessary, we recommend a systematic approach to side effect monitoring. This is often neglected in clinical practice (Fleischhacker, 2009; Haddad et al., 2014; Mitchell et al., 2012). When a clinical intervention is required, it should take into account that both nonpharmacological and pharmacological factors contribute to metabolic side effects (Megna et al., 2011). Nonpharmacological interventions include individual or group psychoeducation, self-monitoring, cognitive behavioral therapy, nutritional intervention, supervised exercise programs, and/or nutritionist and dietician consultations (Caemmerer et al., 2012; Gaughran and Lally, 2013). The first pharmacological intervention is to switch to a less orexigenic antipsychotic (Maayan and Correll, 2010), or to a different ART composition (Samaras, 2008), although the benefit of this change should be weighed against respectively potential worsening of psychopathology (Rosenheck et al., 2009) and drug toxicities/resistances (Samaras, 2008). Adjunctive pharmacological interventions could be targeted to specific metabolic alterations (e.g. fibrate therapy for hypertrigliceridaemia). Different agents (e.g. metformin, stimulants, reboxetine, topiramate) have been studied to prevent or reduce antipsychotics induced-weight gain with only limited evidence of efficacy (Maayan et al., 2010). Metformin could be effective in patients whose weight increases more than 10 kg after the first exposure to antipsychotics (Bjorkhem-Bergman et al., 2011). Additionally metformin was found to improve insulin sensitivity and reduce abdominal obesity in patients taking ART (van Wijk et al., 2005); metformin has limited gastrointestinal side effects and is not metabolized by hepatic P450 enzymes, so it could represent a valid option to avoid drug–drug interactions during concomitant use of ART and SGAs.

Despite these limitations, the findings presented here highlight the need for prospective longitudinal observational and interventional (treatment) studies of metabolic consequences of concurrent SGA and ART use in HIV-infected individuals to understand which combinations of ART drugs and SGAs produce the least metabolic effects and the methods to ameliorate these effects could improve the long-term health of these patients and reduce rates of cardiovascular mortality.

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Appendix A. Supporting information

Supplementary data associated with this paper can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2014.04.015.

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