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ORIGINAL ARTICLE

The Role of Cohort Studies in Drug Development: Clinical Evidence of Antiviral Activity of Serotonin Reuptake Inhibitors and HMG-CoA Reductase Inhibitors in the Central Nervous System

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Abstract *Background*: Effective antiretroviral therapy (ART) has reduced the incidence of HIV-associated neurocognitive impairment (HNCI) but its prevalence remains high. Clinical trials have yet to identify a consistently effective treatment for HNCI, other than ART, but in vitro data support that some drugs approved by the Food and Drug Administration (FDA) for other indications might benefit individuals with HNCI. Some of these drugs, such as serotonin reuptake inhibitors (SRIs) and HMG-CoA reductase inhibitors (statins), may do so by reducing HIV replication in the CNS and are already widely used by HIV-infected individuals. *Methods*: Six-hundred fifty-eight HIV-infected participants of the CHARTER cohort had a baseline assessment, which included comprehensive neuropsychological (NP) testing and HIV RNA measurements in plasma and cerebrospinal fluid (CSF). Four-hundred sixty-seven (71%) subjects used ART, 195 (30%) used SRIs, and 63 (10%) used statins. *Results*: SRI users were less likely to have HIV RNA levels in CSF above 50 copies (c)/mL (29 vs. 37% in non-SRI users, OR 0.69, $p=0.05$). This association was most evident for three of the seven SRIs (citalopram, sertraline, and trazodone, or "antiviral" SRIs, combined 25 vs. 38% in non-SRI users, OR 0.56, $p=0.01$) and was strongest in those not taking concomitant ART (61 vs. 83%, OR 0.31, $p=0.01$). "Antiviral" SRI users also performed better on NP tests (median global deficit score 0.37 vs. 0.47, $p=0.04$). Statin users were also less likely to have HIV RNA levels in CSF above 50 c/mL (16 vs. 37%, $p<0.001$) but, in contrast to SRIs, the association was strongest in those taking ART (2 vs. 18%, $p<0.001$). Statin use was not associated with better NP performance. Multivariate analyses indicated that the use of "antiviral" SRIs—but not statins—was associated with undetectable HIV RNA levels in CSF and better NP performance. *Conclusions*: SRIs may reduce HIV replication in CSF and improve NP performance. This was particularly true for three SRIs—supporting differences in antiviral efficacy between drugs—in individuals who were not taking ART. In contrast, statins were not associated with lower HIV replication in CSF in multivariate analyses and were not

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associated with better NP performance. These analyses support the value of large observational cohort studies in identifying FDA-approved drugs that may be worth further investigation.

Keywords HIV · cerebrospinal fluid · serotonin reuptake inhibitors · statins

Background

Effective antiretroviral therapy (ART) has reduced the incidence of HIV-associated neurocognitive impairment (HNCI) but its prevalence remains high (Sacktor 2002; McArthur et al. 2003; Cysique et al. 2004; Tozzi et al. 2005). This high prevalence reflects the limited CNS effectiveness of ART and the lack of a consistently effective treatment for HNCI that augments ART (Heseltine et al. 1998; No Authors Listed 1998; Schifitto et al. 1999; Sacktor et al. 2000; Clifford et al. 2002). In vitro data support that some drugs approved by the Food and Drug Administration (FDA) for other indications may benefit individuals with HNCI.

Interest has recently focused on minocycline (Zink et al. 2005) and inhibitors of glycogen synthase kinase-3 beta, such as lithium (Gallicchio et al. 1993; Harvey et al. 2002; Dou et al. 2005; Letendre et al. 2006) and valproic acid (Ances et al. 2006; Schifitto et al. 2006). However, these drugs are not commonly prescribed to HIV-infected individuals, limiting preliminary assessment of their impact on outcomes in cohort studies. In contrast, two other classes of approved drugs, serotonin reuptake inhibitors (SRIs) and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), are often prescribed to HIV patients. This is important because both classes of drugs may inhibit HIV replication in vitro but their effects have not been evaluated in humans.

Kristiansen and Hansen (2000), for example, demonstrated that the selective SRIs, paroxetine and femoxetine, reduced p24 levels in an in vitro HIV inhibition cell culture system although the mechanism of action was not identified. Several studies have supported the antiviral activity of statins (Giguere and Tremblay 2004; Mukhtar et al. 2005) although others have not (Moncunill et al. 2005; Negredo et al. 2006). If statins do inhibit HIV replication, they may do so via multiple mechanisms, including reduction of chemokine receptor-containing membrane lipid rafts (Popik et al. 2002; Goebel et al. 2005; Hillyard et al. 2006), adhesion molecule expression (Gilbert et al. 2005), and Rho guanosine triphosphatase activity (del Real et al. 2004). Because both classes of drugs may affect the CNS (Anderson 2004; Schmeer et al. 2006), we hypothesized that they would reduce HIV RNA levels in CSF and be associated with better neuropsychological (NP) performance compared with individuals who took neither class of drug. To test these hypotheses, we analyzed data from individuals enrolled in CHARTER (CNS AntiRetroviral Therapy Effects Research), an NIH-funded, North American cohort designed to assess the impact of HIV and ART on the central nervous system.

Methods

Study description

CHARTER is a multicenter, prospective, observational study designed to recruit a cohort that is similar to the U. S. population of HIV-infected individuals and to determine the effects of ARV therapy on the nervous system. The research was conducted at six North American locations: Johns Hopkins University, Baltimore, MD; Mt. Sinai, New York, NY; University of California, San Diego, CA; University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. The Institutional Review Boards at each site approved the study. The study procedures included comprehensive NP and neuromedical assessments, phlebotomy, lumbar puncture, and other assessments. Subjects (n=658) were included in this analysis if they completed baseline evaluations, had successful lumbar punctures, and had HIV RNA levels measured in both plasma and CSF.

SRI and statin use

Subjects completed a series of questionnaires capturing detailed information about current and past use of SRIs and statins. To increase the reliability of the data collected, subjects were presented with a complete list of available SRIs and statins and asked to indicate whether they had ever used or were currently using each medication.

Neuromedical and laboratory assessments

All subjects underwent standardized neuromedical assessments. AIDS was diagnosed according to 1993 Centers for Disease Control guidelines. Blood was collected by venipuncture and CSF by lumbar puncture. HIV RNA levels were quantified in plasma and CSF by reverse transcriptase-polymerase chain reaction (Amplicor®, Roche Diagnostics, Pleasanton, CA, USA) using the ultrasensitive assay (nominal limit of quantitation 50 copies (c)/mL). HIV RNA values were truncated at the lower limit of quantita-

tion for the purpose of analysis ("undetectable"). CD4+ cell counts were measured by flow cytometry.

Neuropsychological assessment

All subjects received a comprehensive NP evaluation, which was constructed to provide a relatively focused, but nonetheless robust, assessment of the cognitive domains known to be impaired in HIV. Specifically, the test battery was comprised of the following measures: (1) Hopkins Verbal Learning Test—Revised (Benedict et al. 1998), (2) Brief Visuospatial Memory Test—Revised (Benedict 1997), (3) Controlled Oral Word Association Test (Gladsjo et al. 1999) (COWAT-FAS), (4) semantic verbal fluency (Gladsjo et al. 1999), (5) Trail Making Test, Parts A and B (Heaton et al. 2004a, b), (6) Wisconsin Card Sorting Test—64 Card Version (WCST-64) (Kongs et al. 2000), (7) Paced Auditory Serial Addition Test (Diehr et al. 1998), (8) Grooved Pegboard Test (Heaton et al. 1991), (9) the Digit Symbol, Symbol Search, and Letter-Number Sequencing Tests from the Wechsler Adult Intelligence Scale—Third Edition (Heaton et al. 2002), and (10) Heaton Story and Figure Memory Tests (Heaton et al. 2004a, b). All NP tests were administered and scored by certified psychometrists in accordance with published procedures.

Raw scores were converted to demographically adjusted *T*-scores (m=50, SD=10) based on published normative data to account for the influence of age, education, sex, and ethnicity when possible (Carey et al. 2004). *T*-scores were then converted into deficit scores according to the following criteria: >40*T*=0, 39*T*–35*T*=1, 34*T*–30*T*=2, 29*T*–25*T*=3, 24*T*–20*T*=4, and ≤19*T*=5. The deficit scores from each of the NP test variables were then averaged to derive a Global Deficit Score (GDS; range=0–5.00) for each participant, whereby higher scores reflect greater levels of impairment. Global impairment was determined by GDS of at least 0.5.

All participants also completed the Beck Depression Inventory=II (BDI) (Beck et al. 1996). The BDI is a 21-item self-report measure that rates severity of depressive symptoms during the past two weeks. Depressive symptoms assessed with the BDI include both somatic (e.g., weight loss, fatigue) and nonsomatic (e.g., suicidal ideation, feelings of guilt) items.

Statistical analysis

Plasma and CSF HIV RNA values were $\log_{10}$-transformed before analysis to improve their distribution. Univariate analyses were performed using Fisher's exact tests for categorical variables (e.g., gender), t tests for normally distributed continuous variables (e.g., age), or Wilcoxon rank sum tests for skewed continuous variables (e.g., HIV RNA). Given the limited number of analyses, no adjustment for multiple comparisons was imposed. Logistic regression was used for multivariate analyses predicting HIV RNA detection in CSF. Linear regression was used for multivariate analyses predicting NP performance. All analyses were performed using JMP (version 6.0, SAS Institute Inc., Cary, NC, USA).

Results

Participant characteristics

Of 658 subjects, 467 (71%) reported ARV use, 195 (30%) reported SRI use, and 63 (10%) reported statin use at the time of their study visit. HIV RNA levels were detectable in plasma for 383 (58%) subjects and in CSF for 230 (35%) subjects. The median CD4 count was 402 cells/μL, and 64% of subjects had a diagnosis of AIDS.

Table 1 lists the seven SRIs reported by participants. SRI users endorsed more severe symptoms of depression on the BDI than nonusers (median BDI score [interquartile range (IQR)]: 16 [9–26] vs. 11 [5–20], p<0.001). They were also more likely to be Caucasians (53 vs. 38%, p<0.01) and female (26 vs. 18%, p=0.03) but had similar levels of age and education. SRI users were more likely to be prescribed with ARVs (77 vs. 70%, p=0.06), have higher CD4 counts (median [IQR] in cells per microliter: 433 [267–635] vs. 389 [229–565], p=0.07), and have lower HIV RNA levels in plasma (median [IQR] in $\log_{10}$ copies per milliliter: 1.9 [1.7–3.5] vs. 2.4 [1.7–4.8], p=0.07). SRI use was not associated with nadir CD4 count or AIDS diagnosis.

Table 1 also lists the five statins reported by participants. Compared to nonusers, statin users had higher CD4 counts (median [IQR] in cells per microliter: 499 [342–726] vs. 392 [237–576], p<0.01) and lower HIV RNA levels in plasma (median [IQR] in $\log_{10}$ copies per milliliter: 1.7 [1.7–2.5] vs. 2.4 [1.7–4.1], p<0.001). Statin users were also older (mean age in years [SD]: 49 (7) vs. 43 (8), p<0.001), better educated (mean years of education [SD]: 14 (3) vs. 12 (2), p<0.001), and more likely to be Caucasians (59 vs. 41%, p<0.01) compared to nonstatin users. Additional demographic and clinical details are provided in Table 1.

SRI or statin use and HIV RNA in CSF

SRI users were less likely to have detectable HIV RNA in CSF compared to nonusers (29 vs. 37%, OR=0.69, p=0.05) although this relationship only trended toward significance when HIV RNA levels were expressed as a continuous variable (median [IQR] in $\log_{10}$ copies per milliliter: 1.7 [1.7–2.0] vs. 1.7 [1.7–2.5], p=0.06). When individual drugs were analyzed for their relationship to HIV RNA levels in CSF, three drugs trended toward associations

Table 1 Demographic and clinical characteristics

	SRI users	SRI nonusers	Statin users	Statin nonusers
Sample size	195	464	63	596
Gender, no. of males (%)	*144 (74%)	*379 (82%)	55 (87%)	468 (78%)
Age, mean years (SD)	43 (8)	43 (8)	*49 (7)	*43 (8)
Ethnicity, no. of Caucasians (%)	*103 (53%)	*177 (38%)	*37 (59%)	*243 (40%)
Education, mean years (SD)	13 (3)	12 (2)	*14 (3)	*12 (2)
AIDS: no. (%)	125 (64%)	298 (64%)	46 (74%)	377 (63%)
CD4 current: median (IQR)	430 (265–635)	389 (229–565)	*499 (342–726)	*392 (237–576)
CD4 nadir: median (IQR)	196 (56–304)	157 (42–283)	172 (47–258)	160 (47–287)
BDI: median (IQR)	*16 (9–26)	*11 (5–20)	12 (6–24)	12 (6–22)
ART users: no. (%)	151 (77%)	326 (70%)	51 (83%)	416 (71%)
HIV RNA				
Plasma, median (IQR)	*1.9 (1.7–3.5)	*2.4 (1.7–4.1)	*1.7 (1.7–2.5)	*2.4 (1.7–4.1)
Plasma, *n* (%) above 50 c/mL	107 (55%)	276 (59%)	*23 (36%)	*360 (60%)
CSF, median (IQR)	1.7 (1.7–2.0)	1.7 (1.7–2.5)	*1.7 (1.7–1.7)	*1.7 (1.7–2.5)
CSF, *n* (%) above 50 c/mL	*57 (29%)	*173 (37%)	*10 (16%)	*220 (37%)
SRI users, no. (%)	195 (100%)	0 (0%)	*27 (43%)	*168 (28%)
Trazodone	64 (33%)	–	9 (14%)	55 (9%)
Paroxetine	39 (20%)	–	3 (5%)	36 (6%)
Sertraline	37 (19%)	–	7 (11%)	30 (5%)
Venlafaxine	26 (13%)	–	3 (5%)	23 (4%)
Citalopram	24 (12%)	–	2 (3%)	22 (4%)
Escitalopram	22 (11%)	–	4 (6%)	18 (3%)
Fluoxetine	21 (11%)	–	3 (5%)	18 (3%)
Statin users: no. (%)	*27 (14%)	*36 (8.1%)	63 (100%)	0 (0%)
Atorvastatin	17 (9%)	25 (3%)	42 (66.7%)	–
Pravastatin	*10 (5.1%)	*8 (1.7%)	18 (29%)	–
Simvastatin	2 (1%)	2 (0.4%)	4 (6.4%)	–
Fluvastatin	1 (0.5%)	1 (0.2%)	2 (3.2%)	–
Lovastatin	1 (0.5%)	0 (0%)	1 (1.6%)	–

The number of individual SRI sums to 233 since 38 subjects reported use of two SRIs. The number of individual statins sums to 67 since 4 subjects reported use of two statins. HIV RNA levels are expressed as $\log_{10}$ copies per milliliter. SD=Standard deviation, IQR=interquartile range
*$p \leq 0.05$

with lower HIV RNA levels in CSF [citalopram (n=24, p=0.10), trazodone (n=64, p=0.09), and sertraline (n=37, p=0.11)]. Combining users of these three drugs into an "antiviral" SRI category (n=125) strengthened the association with HIV RNA in CSF (median [IQR] in $\log_{10}$ copies per milliliter: 1.7 [1.7–1.7] vs. 1.7 [1.7–2.5], p=0.05; 25% detectable vs. 37% in non-SRI users, OR=0.56, p=0.02). Statin users also had lower HIV RNA levels in CSF (median [IQR] in $\log_{10}$ copies per milliliter: 1.7 [1.7–1.7] vs. 1.7 [1.7–2.5], p<0.01) and had less than half the odds of having detectable HIV RNA levels in CSF as nonstatin users (16 vs. 37%, OR=.32, p<0.001). Subjects who reported use of more than one SRI (n=33) or more than one statin (n=7) did not have significantly lower HIV RNA levels in CSF than those who reported use of only one drug in each class.

Four groups were defined by combining use of "antiviral" SRIs and statins (Neither, SRI Only, Statin Only, and SRI+Statin). HIV RNA levels in CSF differed among the four groups (mean in $\log_{10}$ copies per milliliter: 2.2 Neither vs. 2.1 SRI Only vs. 2.0 Statin Only vs. 1.8 SRI+Statin, ANOVA p=0.03; proportion greater than 50 c/mL: see Fig. 1). Pairwise comparisons indicated that only the "SRI + Statin" group had lower HIV RNA levels in CSF than the "Neither" group (OR=0.21, p=0.02).

To determine whether ART accounted for the observed relationships between SRI or statin use and HIV RNA levels in CSF, analyses were stratified by ART use (Fig. 2). Among subjects using ARVs, statin users were much less likely to have detectable HIV RNA in CSF than nonstatin users (2% detectable vs. 18%, OR=0.09, p<0.001). In contrast, "antiviral" SRIs were more strongly associated with lower HIV RNA levels in CSF among subjects not using ARVs. In this group, "antiviral" SRI users had less than half the odds of having detectable HIV RNA in CSF as non-SRI users (61% detectable vs. 83%, OR=0.31, p=0.01).

To determine whether other factors might account for the observed relationships, a series of logistic regressions was

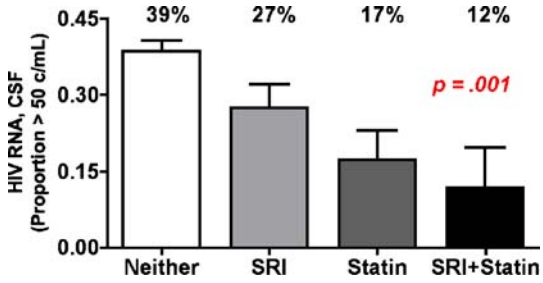

Fig. 1 Combined Effects of SRIs and statins on HIV RNA levels in CSF. The use of SRIs and statins seemed to be additively associated with lower proportions of HIV RNA levels >50 c/mL. ART use did not differ between the four groups ($p>0.10$).

performed evaluating the variance in HIV RNA levels in CSF explained by AIDS diagnosis, ART use, CD4 count, HIV RNA levels in plasma, BDI, education, age, gender, and ethnicity. In the best-fit model, undetectable HIV RNA levels in CSF were associated with the use of "antiviral" SRIs (OR=0.72, $p<0.05$), ART use ($p<0.001$), lower CD4 counts ($p<0.01$), undetectable HIV RNA levels in plasma ($p<0.001$), and Caucasian ethnicity ($p=0.02$) but not the use of statins ($p=0.09$) (model $R^2=0.46$, $p<0.001$).

SRI or statin use and NP impairment

Users of "antiviral" SRIs performed better on NP testing, whether measured as better global deficit scores (median [IQR]: 0.37 [0.16–0.94] vs. 0.47 [0.26–1.00], $p=0.04$) or a lower proportion of impairment (55 vs. 64%, $p=0.05$). Statin use was not associated with NP performance or impairment status. In a linear regression model predicting global deficit scores and adjusting for AIDS diagnosis, ART use, CD4 count, plasma and CSF HIV RNA, education, age, gender, ethnicity, and BDI, only the use of "antiviral" SRIs was significantly associated with normal NP performance ($p=0.03$).

Discussion

The current analysis supports further evaluation of three SRIs (citalopram, sertraline, and trazodone) and perhaps statins (predominantly atorvastatin and pravastatin in this cohort) for their antiviral and central nervous system effects. This is important because effective treatments for HIV-associated neurocognitive disorders remain an important unmet medical need based on the high prevalence in untreated and treated populations in both developed and resource-limited settings. Drug development efforts for HNCI have slowed for a number of reasons, including shifting patterns of disease and antiretroviral prescribing practices, challenges in assessment and diagnosis, and the limited success of prior trials. Observational cohort studies can support drug development by confirming—or refuting—the effectiveness of drugs that are used in a sufficiently large proportion of the cohort.

Our analysis demonstrated that individuals who took SRIs were more likely to have undetectable HIV RNA levels in CSF and better global NP performance. A plausible explanation for these effects is that SRI use resulted in better mood, resulting in better antiretroviral adherence or better effort on NP testing. Several facts argue against this hypothesis. First, better mood was not associated with undetectable HIV RNA levels in CSF or better NP performance (data not shown), arguing that this was not the mediator between these measures and SRI use. Second, SRI use was associated with lower HIV RNA levels in CSF predominantly among individuals who were not using ART, arguing strongly against the adherence theory. Third, only three SRIs were associated with undetectable HIV RNA levels in CSF and better NP performance, drug-specific effects that argue against attribution to the improvements in mood that all SRI drugs are designed to yield. Fourth, SRI use remained independently associated with undetectable HIV RNA levels in CSF even after adjusting for mood, antiretroviral use, and other disease-related measures. Together, these facts refute the hypothesis that better mood explained the findings but instead support a more direct link between SRI use, reduction in HIV RNA in CSF, and NP performance.

Statins were not expected to affect mood or ART adherence, so the observed associations with undetectable HIV RNA levels in CSF are less likely to be confounded. This association, however, only trended toward statistical significance after adjusting for antiretroviral use, SRI use, HIV RNA levels in plasma, and other measures. The effects of statins did not differ for individual drugs although these

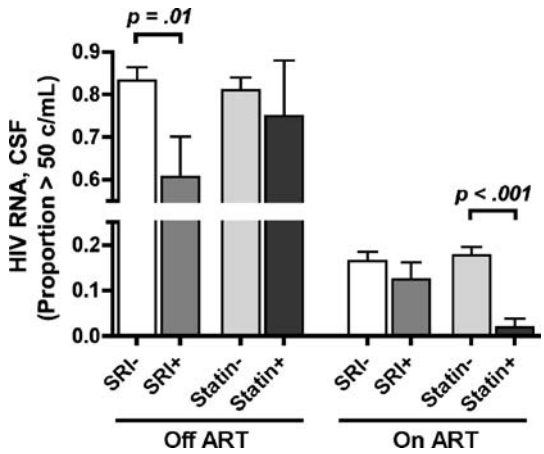

Fig. 2 "Antiviral" SRI users (denoted "SRI" in this graph for simplicity) who did not use ART had less than half the odds of having detectable HIV RNA levels in CSF as non-SRI users (OR= 0.31), and statin users who used ART had less than a tenth the odds of having detectable HIV RNA levels in CSF as nonstatin users (OR= 0.09).

analyses were limited by the relatively low prevalence of statin use in the cohort. In contrast to SRIs, statins were associated with undetectable HIV RNA levels in CSF in ART-treated individuals, suggesting that their effects may be mediated by modifying antiretroviral metabolism or distribution. Several explanations are possible for the observed lack of NP benefit of statins. First, the association between statin use and undetectable HIV RNA levels in CSF could be an artifact due to type-I statistical error or confounding conditions, such as access-to-care. Subjects who used statins, for example, who used more prescription medications (as indexed by SRIs and statins), were more likely to be Caucasians and had more years of education and higher CD4 counts, all of which have been associated with better medical care in the U.S. (Currier and Fliesler 1995; Palacio et al. 2002; Cargill and Stone 2005). Balancing these factors, however, is the fact that statin users and nonusers were followed by the same providers in the same clinics and had similar rates of AIDS and ART use. Second, the benefits conferred by reduced HIV RNA levels might be mitigated by other conditions. In HIV-infected individuals, ART—particularly with certain protease inhibitors like ritonavir—can be complicated by several metabolic disorders, sometimes collectively termed lipodystrophy. When statins are used to treat protease inhibitor-induced lipodystrophy, the NP benefit could be negated by several factors, including the protease inhibitor, the statin, or the lipodystrophy disorder itself. Protease inhibitors, for example, are among the least CNS-penetrating antiretrovirals and, as such, individuals treated with them may have higher HIV RNA levels in CSF and may be at greater risk for HIV-associated neurocognitive disease compared to those taking non-PI combination regimens. Statins have been associated with evidence of brain injury such as memory loss although conflicting data exist (Wagstaff et al. 2003). If statins do injure the brain, this would paradoxically limit the antiviral benefit they confer in HIV-infected individuals. Hyperlipidemia and metabolic disorders have also been linked to higher risk for neurocognitive disease (Evans et al. 2004; Valcour et al. 2005). Because some metabolic disorders, such as lipoatrophy, are associated with mitochondrial injury, this might be a common mechanism linking them with brain injury. While these explanations are plausible, their analysis in this manuscript is limited by the sample size (63 individuals using five different statins). CHARTER aims to address these issues as part of an ongoing metabolic substudy.

The study has important limitations. First, its cross-sectional, observational design may not adequately account for potentially confounding factors, such as pretreatment differences between comparison groups. Second, although the overall sample size is large, only a subset of individuals used the drugs of interest. This was particularly true for statins, which were used in only 10% of the cohort. While this limited the power of the study to detect associations with study outcomes, the adjusted associations still trended toward statistical significance and therefore, if they are confirmed in independent analyses, the effect sizes could be substantial. Third, the current analyses do not include dosing or concentration data for SRIs or statins or adherence data for ART. Such data could modify the relationships with study outcomes. For example, an association between higher concentrations of citalopram and better outcomes would improve confidence in the study's findings. Another notable issue is ART adherence, especially in light of the substantial proportion of non-SRI-using subjects who had symptoms of at least mild depression (median BDI 11). Non-SRI-using subjects who had untreated depression might also have reduced ART adherence, which could lead to ART failure, which, in turn, would tend to confound our analyses. Fourth, possible mechanisms of anti-HIV activity have been postulated for statins but, as yet, none has been identified for SRIs. Until a mechanism of action is identified, our findings must be considered with caution.

Despite these limitations, the findings support further evaluation of the antiviral and neurocognitive benefits of SRIs and possibly statins in HIV-infected individuals. They also reinforce that well-designed cohort studies can provide evidence suggesting additional effects of FDA-approved drugs. This evidence can then be used to focus further investigation. In an environment of rising drug development costs and constrained research budgets, such analyses may leverage pharmaceutical investment, reduce development time and risk, and extend drug indications, ultimately leading to more effective and less expensive treatments for HIV-infected individuals.

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