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Use of non-antiretroviral medications that may impact neurocognition: patterns and predictors in a large, long-term HIV cohort study

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List of Supplemental Digital Content:

- Supplemental Digital Content 1, Table, “NCAE_Supplemental table.doc”

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Abstract

Background—Neurocognitive impairment is a frequent and often disabling comorbidity of HIV infection. In addition to antiretroviral (ARV) therapies, individuals with HIV infection may commonly use non-ARV medications that are known to cause neurocognitive adverse effects (NC-AE). The contribution of NC-AE to neurocognitive impairment is rarely considered in the context of HIV and could explain part of the variability in neurocognitive performance among individuals with HIV.

Setting—Women's Interagency HIV Study (WIHS); a prospective, multisite, observational study of U.S. women with and without HIV.

Methods—After a literature review, 79 medications (excluding statins) with NC-AE were identified and reported by WIHS participants. We examined factors associated with self-reported use of these medications over a 10-year period. Generalized estimating equations for binary outcomes were used to assess socio-demographic, behavioral, and clinical characteristics associated with NC-AE medication use.

Results—3,300 women (71% with HIV) and data from ~42,000 visits were studied. HIV infection was associated with NC-AE medication use (odds ratio =1.52 (95% confidence interval: 1.35–1.71)). After adjustment for HIV infection status, other predictors of NC-AE medication use included having health insurance, elevated depressive symptoms, prior clinical AIDS, non-injection recreational drug use, and an annual household income <$12,000 ($p$'s<0.004). NC-AE medication use was less likely among women who drank 1–7 or 8–12 alcoholic drinks/week (vs. abstaining) (p's<0.04).

Conclusions—HIV infection was associated with NC-AE medication use which may influence determinations of HIV-associated neurocognitive impairment. Providers should consider the impact of NC-AE medications when evaluating patients with HIV and concurrent neurocognitive symptoms.

Keywords

neurocognition; medication; adverse effects; dementia; HIV

INTRODUCTION

Despite effective antiretroviral (ARV) therapy, people living with HIV continue to report memory and mental acuity problems and demonstrate impairment on standard measures of neuropsychological functioning.[1,2] For example, in the Women's Interagency HIV Study (WIHS), HIV-infected (HIV+) women on effective ARVs show persistent vulnerabilities in

global neuropsychological functioning as well as in verbal learning, memory, attention/working memory, and verbal fluency compared to HIV-uninfected (HIV−) women.[3] Moreover, issues in motor function become apparent over time among HIV+ women on ARVs versus HIV− women. Given the persistence of neurocognitive vulnerabilities despite combined antiretroviral therapy (cART) and their relationship to function[4,5], identifying potential contributors to neurocognitive performance is an important clinical priority.

One factor that may influence some of the variability in neuropsychological test performance among HIV+ individuals is the effects of non-ARV medications with known neurocognitive adverse effects (NC-AE) including agents with anticholinergic properties, anxiolytics, antipsychotics, antiepileptics, and opiates.[2,6–11] The possible contribution of non-ARV medications to neurocognitive performance in HIV+ individuals is particularly important to consider since cART recipients are living longer and using multiple non-ARV medications with age.[12,13] On average, HIV+ individuals report using 7–14 non-ARV medications many of which are NC-AE medications.[14–16] Importantly, concomitant medication use or “polypharmacy” is associated with lower performance on rapid screening tests for cognitive impairment in both HIV+[17] and HIV− individuals.[18]

An important first step before investigating NC-AE medication associations with neuropsychological test performance is to: 1) characterize the patterns and prevalence of NC-AE medication use ; 2) determine socio-demographic, behavioral, and clinical predictors of NC-AE medication use; and 3) to determine whether NC-AE medication use predicts HIV-related treatment outcomes. We addressed these aims within the WIHS and hypothesized that HIV-serostatus would predict NC-AE medication use and that NC-AE medication use would predict lower cART adherence and virologic suppression.

METHODS

Participants

All data were prospectively collected at semi-annual WIHS visits; methods were previously published.[19–21] HIV+ and HIV− women were enrolled in the WIHS at any of 11 sites across the United States between 1994 and 2014 (enrollment dates vary by site and study wave). All participants provided written informed consent via human subject’s protection protocols approved by each of the collaborating institutions. Analyzable participant data was limited to WIHS visits with non-ARV medication data available occurring in the era of optimized cART regimens. Specifically, we included 21 visits beginning April 2004 through September 2014 (data available at the time of analysis). Women with incident HIV infection after WIHS enrollment were excluded (n=25).

Data collection

Self-reported socio-demographic and medication use data were obtained via interviewer-administered survey instruments, and HIV-relevant laboratory measurements were recorded from specimen analysis at study visits.[20] For medication use, participants were asked to recall ARV medications taking currently and since last study visit (typically six months),

medications for specific conditions of interest, and any other medications used since last visit.

Defining NC-AE medication use

A literature search was conducted using UpToDate® and PubMed® to identify non-ARV NC-AE medications. The search included a combination of terms related to central nervous system (CNS) impairment (e.g., "cognit* AND impair*"), medication use (e.g., "med*", "drug"), and adverse effects (e.g., "adverse"). Medication classes (e.g., antidepressants) identified through this search were further explored through additional, more specific search terms. In order for a medication to make NC-AE classification, reports must have described the specific adverse effect (e.g., memory loss) associated with a specific medication. Medications with CNS adverse effects but not those impairing cognition (e.g., headache) were not accepted as NC-AE classification. Both primary and review articles were accepted as sources. The NC-AE for each identified medication was verified using a second resource, Lexicomp Online.

Using these methods, 102 non-ARV medications were identified as having NC-AE properties and 83/102 were reported to be used by WIHS participants. Each NC-AE medication was assigned an individual code as well as one group code determined by the medication's drug class. Earlier studies report that hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) were associated with neurocognitive impairment; however, recent systematic assessments indicate that statins are not likely to cause neurocognitive impairment and could possibly prevent it.[22–24] The association between statin use and neurocognitive impairment is most likely due to their major indication of the treatment of hyperlipidemias, a condition that increases the risk of vascular-based neurological injury[25] We suspect that statins likely differ from other NC-AE medications that have more direct effects on cognition. Thus, we excluded statins from the list of NC-AE medications, leaving 79 NC-AE medications in 11 classification groups (see Table, Supplemental Digital Content 1, for list of NC-AE medications). Each potential NC-AE medication identified in the WIHS dataset was further ascertained by a Doctor of Pharmacy candidate (K.R.) to ensure accurate NC-AE classifications. The WIHS database was searched by brand name, generic name, and indication as well as potential variations in spellings of NC-AE medication names. Individual participants were classified as an ever (versus never) NC-AE medication user based on whether they reported using at least one NC-AE medication at any time. Visits were considered an NC-AE medication use visit if at least one NC-AE medication was reported.

Predictors of NC-AE medication use

Fixed-factors were summarized by unique WIHS participant (N=3,300) and included HIV infection status, race/ethnicity, enrollment site, and educational attainment (high school/GED/diploma). Time-varying factors were summarized by unique WIHS visit and included: age, annual household income (>$12,000), injection and non-injection recreational drug use (RDU), alcohol use (abstain, 1–7 drinks/week, 8–12 drinks/week, or >12 drinks/week), elevated depressive symptoms (Center for Epidemiologic Studies Depression Scale ≥ 16), homelessness (residence of street, shelter/welfare hotel, or rooming/boarding/halfway

house), third-party health payer (any private/public health or dental insurance or medication cost assistance payer), clinical AIDS (any criterion excluding CD4 cell count), and undetectable plasma HIV RNA (values below assay threshold ranged from 50–80cp/ml during the study period).

Statistical Analyses

Basic summary statistics (e.g., mean, standard deviation) were used to summarize participant characteristics. Generalized estimating equations for discrete outcomes were conducted to assess factors associated with any NC-AE medication use and to assess any NC-AE medication use as a predictor of HIV-related clinical outcomes including cART use, ≥ 95% cART adherence, undetectable plasma HIV RNA (viral load). All models were fit using PROC GENMOD (exchangeable correlation structure) in SAS version 9.4 (SAS Institute, Cary, NC). Significance was set at $p<0.05$.

RESULTS

Participants

A total of 3,300 women and 42,281 visits met inclusion criteria (Table 1). Due to missing non-ARV medication data, 661 visits (487 HIV+; 74 HIV−) were excluded from analyses. Of the 3,300 women, 2,328 (71%) women were HIV+. Among HIV+ women, ≥95% adherence to cART was common (82% of visits), viral load was undetectable at 50% of visits, 41% had a history of clinical AIDS, and the lowest median CD4 count at any WIHS visit was 200 cells/mm^3 (interquartile range 87–319). Missing data for each variable comprised <10% of visits with the exception of income (11% HIV+; 13% HIV−).

Patterns of NC-AE medication use

Overall, HIV+ women reported NC-AE medication use more often than HIV− women (42% of visits vs. 30%). When all visits were considered (NC-AE medication use and non-use visits), HIV+ women reported greater use of anxiolytic, opioid, antihistamine, gastrointestinal (e.g., loperamide), and antidepressant NC-AE medications versus HIV− women (p's<0.001; Table 2).

Predictors of NC-AE medication use

In unadjusted models, HIV+ women were more likely to use NC-AE medications compared to uninfected women ($p<0.0001$; Table 3). A history of clinical AIDS was also a predictor of NC-AE medication use among HIV+ women ($p<0.0001$). After adjusting for HIV-serostatus, predictors of NC-AE medication use included: having a third-party health payer, elevated depressive symptoms, and non-injection RDU (p's<0.01). Annual household income >$12,000 and non-hazardous alcohol consumption (1–7 and 8–12 drinks/week) were associated with being less likely to report NC-AE medication use (p's<0.05).

NC-AE medication use and HIV-related treatment outcomes

NC-AE medication use at a WIHS visit was a significant predictor of cART use and having an undetectable viral load at that visit (p's<0.001; Table 4). However, a significant association of NC-AE medication use with cART adherence was not found (p=0.45).

DISCUSSION

To our knowledge, this is the first study to examine patterns and predictors of use of non-ARV medications with known neurocognitive effects, as well as the impact on HIV-related treatment outcomes. HIV+ women were more likely to report using any NC-AE medications compared to HIV− women, specifically antianxiety, opioid, gastrointestinal (primarily antidiarrheal agents), antihistamines and antidepressant medications, all of which are commonly prescribed in HIV practices.[26–28] Thus, the differential use of non-ARV NC-AE medications could explain some of the variability in neurocognitive performance in studies examining HIV-associated cognitive impairment.

HIV+ NC-AE medication users in the current study were more likely to use cART than non-NC-AE medication users. This finding is consistent with a previous WIHS study where non-ARV medication users, specifically antidepressant users, were more likely to use cART.[29] These findings suggest that use of one prescription medication likely predicts use of other prescribed medications and that use of NC-AE medications appears to occur in the context of ongoing medical care. WIHS is a long-term cohort study during which participants engage with staff who encourage linkages to care, particularly when severe symptoms or lab abnormalities are present; thus, the participants analyzed in this study may be more likely to enter care than individuals who do not participate in a study similar to the WIHS. Receipt of these treatments requires either financial ability to self-pay or health plan coverage for medication costs. The latter is in accordance with our findings that having a health plan predicted NC-AE medication use. However, higher annual incomes (>$12,000) were associated with no NC-AE medication use in our study. While incomes above $12,000 per year might be expected to result in greater ability to pay for medications, higher incomes are likely the result of employment which may be associated with lower mental illness and thus, lower need for use of many of the medications with NC-AE classification.

Abstaining from alcohol use was associated with greater likelihood of NC-AE medication use in our study. This finding could be explained by the recommended avoidance of alcohol with many of the NC-AE medications (e.g., zolpidem, opioids, benzodiazepines) and/or the result of alcohol consumption replacing the need for NC-AE medication use. Recent injection RDU was not common in the cohort, and thus our study had a wide confidence interval for its relation to use of NC-AE medications. However, non-injection RDU was associated with NC-AE medication use, perhaps the result of the widely recognized association between mental illness and RDU or influenced by the inclusion of opioids in the NC-AE category as opioids can be both prescribed and abused for recreational purposes including self-medication for symptom management.[30]

While the literature regarding the link between non-ARV medication use and neurocognitive impairment in HIV+ individuals is limited; medical conditions that warrant the use of NC-

AE medications have been linked to HIV-associated cognitive impairment as well as poor health outcomes. For example, depression, RDU, and stress-disorders are all associated with cognitive vulnerabilities in HIV+ individuals.[31–36] Psychiatric disorders and serious mental illness are also associated with poor HIV outcomes.[37–41] Additionally, high concomitant medication use may be risk factors for cognitive decline and increased mortality in HIV-uninfected adults.[18,42–44] While the directionality of these findings are unknown, it is important to consider concomitant medication use, especially in the case of HIV infection where individuals automatically acquire at minimum three medications upon diagnosis for HIV treatment alone.[44–47] Future studies evaluating the relationship between non-ARV medication use and cognitive function in individuals living with HIV should also control for psychiatric comorbidities and sociodemographic factors (e.g., RDU).

We predicted that NC-AE medication use would be associated with worse HIV-treatment outcomes (e.g., high viral load) secondary to potential medication effects on cognition. In contrast, NC-AE medication use was associated with beneficial HIV outcomes. These results may be, at least in part, the result of medical referrals made at the time of WIHS visits or treatment of mental illness. Again, causality cannot be determined given that the data were analyzed retrospectively and relied on self-reported medication use. It is possible that cognitive deficits could have reduced recall of medications used, particularly among HIV+ participants, and thus our findings may be a conservative estimate of the relationship between NC-AE medication use and HIV infection. Investigation of the cognitive burden of NC-AE medication use is currently underway and is an important next step to better understand the best strategies to manage complex HIV-specific and non-HIV associated morbidities.

CONCLUSION

The use of NC-AE medications in women living with HIV is high and more common than in women without HIV infection. NC-AE medication use also appears to be associated with cART use and viral suppression in HIV+ women. The causal direction of these associations remains unclear. Further research is needed to determine if NC-AE medication use exacerbates neurocognitive impairment or if discontinuation of NC-AE medications in cognitively impaired HIV+ individuals leads to improved function. Nonetheless, results from this work further the understanding of non-ARV medication use patterns among HIV+ women. The benefits and harms of NC-AE medications are important clinical considerations for the treatment of comorbid conditions in HIV+ individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Schouten J, Cinque P, Gisslen M, Reiss P, Portegies P. HIV-1 infection and cognitive impairment in the cART era: a review. AIDS. 2011; 25(5):561–575. [PubMed: 21160410]
2. Shah A, Gangwani MR, Chaudhari NS, Glazyrin A, Bhat HK, Kumar A. Neurotoxicity in the Post-HAART Era: Caution for the Antiretroviral Therapeutics. Neurotox Res. 2016; 30(4):677–697. [PubMed: 27364698]
3. Rubin LH, Maki PM, Springer G, et al. Cognitive trajectories over 4 years among HIV-infected women with optimal viral suppression. Neurology. 2017; 89(15):1594–1603. [PubMed: 28904086]
4. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc. 2004; 10(3):317–331. [PubMed: 15147590]
5. Thames AD, Kim MS, Becker BW, et al. Medication and finance management among HIV-infected adults: the impact of age and cognition. J Clin Exp Neuropsychol. 2011; 33(2):200–209. [PubMed: 20694873]
6. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS drugs. 2004; 18(1):37–48. [PubMed: 14731058]
7. Mintzer MZ, Griffiths RR. Triazolam and zolpidem: effects on human memory and attentional processes. Psychopharmacology (Berl). 1999; 144(1):8–19. [PubMed: 10379619]
8. Hindmarch I. Cognitive toxicity of pharmacotherapeutic agents used in social anxiety disorder. International journal of clinical practice. 2009; 63(7):1085–1094. [PubMed: 19570125]
9. Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology. 2010; 75(2):152–159. [PubMed: 20625168]
10. Eddy CM, Rickards HE, Cavanna AE. The cognitive impact of antiepileptic drugs. Ther Adv Neurol Disord. 2011; 4(6):385–407. [PubMed: 22164192]
11. Ersche KD, Clark L, London M, Robbins TW, Sahakian BJ. Profile of executive and memory function associated with amphetamine and opiate dependence. Neuropsychopharmacology. 2006; 31(5):1036–1047. [PubMed: 16160707]
12. Moore HN, Mao L, Oramasionwu CU. Factors associated with polypharmacy and the prescription of multiple medications among persons living with HIV (PLWH) compared to non-PLWH. AIDS Care. 2015; 27(12):1443–1448. [PubMed: 26608408]
13. Gleason LJ, Luque AE, Shah K. Polypharmacy in the HIV-infected older adult population. Clin Interv Aging. 2013; 8:749–763. [PubMed: 23818773]

14. Greene M, Steinman MA, McNicholl IR, Valcour V. Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. J Am Geriatr Soc. 2014; 62(3):447–453. [PubMed: 24576251]
15. Gimeno-Gracia M, Crusells-Canales MJ, Javier Armesto-Gomez F, Rabanaque-Hernandez MJ. Prevalence of concomitant medications in older HIV+ patients and comparison with general population. HIV Clin Trials. 2015; 16(3):117–124. [PubMed: 25978302]
16. Furler MD, Einarson TR, Walmsley S, Millson M, Bendayan R. Polypharmacy in HIV: impact of data source and gender on reported drug utilization. AIDS Patient Care STDS. 2004; 18(10):568–586. [PubMed: 15630785]
17. Koenig N, Fujiwara E, Gill MJ, Power C. Montreal Cognitive Assessment Performance in HIV/AIDS: Impact of Systemic Factors. Can J Neurol Sci. 2016; 43(1):157–162. [PubMed: 26635008]
18. Jyrkka J, Enlund H, Lavikainen P, Sulkava R, Hartikainen S. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. Pharmacoepidemiol Drug Saf. 2011; 20(5):514–522. [PubMed: 21308855]
19. Bacon MC, von Wyl V, Alden C, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol. 2005; 12(9):1013–1019. [PubMed: 16148165]
20. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. Epidemiology. 1998; 9(2):117–125. [PubMed: 9504278]
21. Hessol NA, Weber KM, Holman S, et al. Retention and attendance of women enrolled in a large prospective study of HIV-1 in the United States. J Womens Health (Larchmt). 2009; 18(10):1627–1637. [PubMed: 19788344]
22. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med. 2013; 159(10):688–697. [PubMed: 24247674]
23. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016; (1):CD003160. [PubMed: 26727124]
24. Kostis JB, Rosen RC, Wilson AC. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. J Clin Pharmacol. 1994; 34(10):989–996. [PubMed: 7836550]
25. McFarland AJ, Anoopkumar-Dukie S, Arora DS, et al. Molecular mechanisms underlying the effects of statins in the central nervous system. Int J Mol Sci. 2014; 15(11):20607–20637. [PubMed: 25391045]
26. Turner AN, Maierhofer C, Funderburg NT, et al. High levels of self-reported prescription opioid use by HIV-positive individuals. AIDS Care. 2016; 28(12):1559–1565. [PubMed: 27320493]
27. Jeevanjee S, Penko J, Guzman D, Miaskowski C, Bangsberg DR, Kushel MB. Opioid analgesic misuse is associated with incomplete antiretroviral adherence in a cohort of HIV-infected indigent adults in San Francisco. AIDS Behav. 2014; 18(7):1352–1358. [PubMed: 24077929]
28. Clay PG, Crutchley RD. Noninfectious Diarrhea in HIV Seropositive Individuals: a Review of Prevalence Rates, Etiology, and Management in the Era of Combination Antiretroviral Therapy. Infect Dis Ther. 2014; 3(2):103–122. [PubMed: 25388760]
29. Cook JA, Grey D, Burke-Miller J, et al. Effects of treated and untreated depressive symptoms on highly active antiretroviral therapy use in a US multi-site cohort of HIV-positive women. AIDS Care. 2006; 18(2):93–100. [PubMed: 16338766]
30. Chander G, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. Drugs. 2006; 66(6):769–789. [PubMed: 16706551]
31. Rubin LH, Cook JA, Weber KM, et al. The association of perceived stress and verbal memory is greater in HIV-infected versus HIV-uninfected women. J Neurovirol. 2015; 21(4):422–432. [PubMed: 25791344]
32. Rubin LH, Pyra M, Cook JA, et al. Post-traumatic stress is associated with verbal learning, memory, and psychomotor speed in HIV-infected and HIV-uninfected women. J Neurovirol. 2016; 22(2):159–169. [PubMed: 26404435]

33. Rubin LH, Wu M, Sundermann EE, et al. Elevated stress is associated with prefrontal cortex dysfunction during a verbal memory task in women with HIV. J Neurovirol. 2016; 22(6):840–851. [PubMed: 27094924]
34. Meyer VJ, Rubin LH, Martin E, et al. HIV and recent illicit drug use interact to affect verbal memory in women. J Acquir Immune Defic Syndr. 2013; 63(1):67–76. [PubMed: 23392462]
35. Maki PM, Rubin LH, Valcour V, et al. Cognitive function in women with HIV: findings from the Women's Interagency HIV Study. Neurology. 2015; 84(3):231–240. [PubMed: 25540304]
36. Vance DE, Rubin LH, Valcour V, Waldrop-Valverde D, Maki PM. Aging and Neurocognitive Functioning in HIV-Infected Women: a Review of the Literature Involving the Women's Interagency HIV Study. Curr HIV/AIDS Rep. 2016; 13(6):399–411. [PubMed: 27730446]
37. Cook JA, Grey D, Burke J, et al. Depressive symptoms and AIDS-related mortality among a multisite cohort of HIV-positive women. Am J Public Health. 2004; 94(7):1133–1140. [PubMed: 15226133]
38. Nurutdinova D, Chrusciel T, Zeringue A, et al. Mental health disorders and the risk of AIDS-defining illness and death in HIV-infected veterans. AIDS. 2012; 26(2):229–234. [PubMed: 22089375]
39. Hartzell JD, Janke IE, Weintrob AC. Impact of depression on HIV outcomes in the HAART era. J Antimicrob Chemother. 2008; 62(2):246–255. [PubMed: 18456650]
40. Farinpour R, Miller EN, Satz P, et al. Psychosocial risk factors of HIV morbidity and mortality: findings from the Multicenter AIDS Cohort Study (MACS). J Clin Exp Neuropsychol. 2003; 25(5):654–670. [PubMed: 12815503]
41. Wada N, Jacobson LP, Cohen M, French A, Phair J, Munoz A. Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984–2008. Am J Epidemiol. 2013; 177(2):116–125. [PubMed: 23287403]
42. Nobili A, Licata G, Salerno F, et al. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. Eur J Clin Pharmacol. 2011; 67(5):507–519. [PubMed: 21221958]
43. Shah BM, Hajjar ER. Polypharmacy, adverse drug reactions, and geriatric syndromes. Clin Geriatr Med. 2012; 28(2):173–186. [PubMed: 22500537]
44. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The next therapeutic challenge in HIV: polypharmacy. Drugs Aging. 2013; 30(8):613–628. [PubMed: 23740523]
45. Krentz HB, Cosman I, Lee K, Ming JM, Gill MJ. Pill burden in HIV infection: 20 years of experience. Antivir Ther. 2012; 17(5):833–840. [PubMed: 22358155]
46. Krentz HB, Gill MJ. The Impact of Non-Antiretroviral Polypharmacy on the Continuity of Antiretroviral Therapy (ART) Among HIV Patients. AIDS Patient Care STDS. 2016; 30(1):11–17. [PubMed: 26544766]
47. Cantudo-Cuenca MR, Jimenez-Galan R, Almeida-Gonzalez CV, Morillo-Verdugo R. Concurrent use of comedications reduces adherence to antiretroviral therapy among HIV-infected patients. J Manag Care Spec Pharm. 2014; 20(8):844–850. [PubMed: 25062078]

Table 1

Demographic characteristics of WIHS study participants from 2004–2014

1a. Characteristics of individual women	**HIV-infected N= 2328 women**	**HIV-uninfected N= 972 women**
Race, n (%)		
White *	300 (12.9)	102 (10.5)
Black *	1419 (60.9)	624 (64.2)
Hispanic	534 (22.9)	207 (21.3)
Other *	75 (3.2)	39 (4.0)
Completed high school, n (%)	1462 (62.8)	657 (67.6)
Enrollment site, n (%)		
Bronx, NY	344 (14.8)	162 (16.7)
Brooklyn, NY	345 (14.8)	138 (14.2)
Chicago, IL	313 (13.5)	102 (10.5)
Washington, DC	309 (13.3)	126 (13.0)
San Franciso, CA	327 (14.0)	140 (14.4)
Los Angeles, CA	373 (16.0)	131 (13.5)
Miami, FL	35 (1.5)	36 (3.7)
Atlanta, GA	90 (3.9)	73 (7.5)
Birmingham, GA	57 (2.4)	23 (2.4)
Jackson, MS	52 (2.2)	16 (1.6)
Chapel Hill, NC	83 (3.6)	25 (2.6)

1b. Characteristics of women at study visits	**HIV-infected** N= 29800 visits	**HIV-uninfected** N= 12481 visits
Age, mean ± SD	46.0 ± 9.0	42.8 ± 10.4
Age, median (IQR)	46.0 (39.7–52.0)	42.8 (34.9–50.1)
Homeless, n (%)	544 (1.8)	406 (3.3)
Annual household income > $12,000, n (%)	13130 (44.1)	5847 (46.8)
Signficant depressive symptoms, n (%)	9363 (31.4)	3472 (27.8)
Alcohol use per week, n (%)		
Abstain	16377 (55.0)	5105 (40.9)
1–7 drinks/week	8887 (29.8)	4401 (35.3)
8–12 drinks/week	940 (3.2)	661 (5.3)
>12 drinks/week	1476 (5.0)	1262 (10.1)
Recreational drug use, current, n (%)		
Non-injection	5246 (17.6)	3327 (26.7)
Injection	363 (1.2)	238 (1.9)

Percentages reflect number of women (1a) or visits (1b) with a particular characteristic out of all women (1a) or all visits (1b) by HIV status.

*=non-Hispanic.

IQR= interquartile range. SD= standard deviation.

Table 2

HIV status as a predictor for NC-AE medication use by medication class

Medication Class	HIV-infected n visits (%)	HIV-uninfected n visits (%)	OR (95% CI)	*p*-value
Anticonvulsant	1274 (4.3)	450 (3.6)	0.96 (0.74–1.24)	0.74
Antianxiety	3706 (12.4)	1047 (8.4)	1.41 (1.17–1.70)	0.0004
Anticholinergic	676 (2.3)	218 (1.7)	1.20 (0.86–1.67)	0.29
Antipsychotic	2074 (7.0)	903 (7.2)	0.93 (0.76–1.15)	0.52
Amphetamine	78 (0.3)	34 (0.3)	0.79 (0.28–2.20)	0.66
Opioid	3420 (11.5)	1102 (8.8)	1.35 (1.15–1.60)	0.0003
Beta Blocker	1004 (3.4)	304 (2.4)	1.29 (0.90–1.86)	0.17
Gastrointestinal	807 (2.7)	186 (1.5)	1.78 (1.27–2.50)	0.0009
Antihistamine	2053 (6.9)	645 (5.2)	1.42 (1.17–1.73)	0.0004
Muscle Relaxant	718 (2.4)	316 (2.5)	0.87 (0.66–1.16)	0.35
Antidepressant	6231 (20.9)	1539 (12.3)	1.58 (1.35–1.85)	<0.0001

HIV-uninfected visits were used as the reference group. OR= odds ratio. CI= confidence interval.

Table 3

Predictors of NC-AE medication use at WIHS visit

Predictors		NC-AE medication use/visits	(%)	OR (95% CI)	*p*-value	Adjusted for HIV status	
						aOR (95% CI)	*p*-value
HIV-infected	No	3739/12481	(30.0)	1.52 (1.35–1.71)	<0.0001		
	Yes	12422/29800	(41.7)				
Third-party health payer	No	764/3842	(19.9)	1.55 (1.43–1.68)	<0.0001	1.54 (1.41–1.67)	<0.0001
	Yes	14332/35435	(40.4)				
Annual household income >$12,000	No	8462/18409	(46.0)	0.84 (0.79–0.88)	<0.0001	0.83 (0.79–0.88)	<0.0001
	Yes	5902/18977	(31.1)				
Homeless	No	14573/38327	(38.0)	1.14 (0.99–1.31)	0.079	1.15 (0.99–1.33)	0.062
	Yes	525/950	(55.3)				
Completed high school	No	5963/15294	(39.0)	0.92 (0.82–1.03)	0.15	0.94 (0.84–1.05)	0.25
	Yes	10168/26881	(37.8)				
Elevated depressive symptoms	No	8005/25974	(30.8)	1.27 (1.21–1.33)	<0.0001	1.27 (1.21–1.33)	<0.0001
	Yes	6825/12835	(53.2)				
Injection RDU	No	14666/38493	(38.1)	0.98 (0.77–1.25)	0.85	0.99 (0.77–1.26)	0.91
	Yes	324/601	(53.9)				
Non-injection RDU	No	10909/30525	(35.7)	1.10 (1.02–1.17)	0.008	1.11 (1.03–1.19)	0.0036
	Yes	4082/8573	(47.6)				
Alcohol use[°]	No	8607/21482	(40.1)	Reference		Reference	
1–7 drinks/week	Yes	4664/13288	(35.1)	0.92 (0.87–0.97)	0.0009	0.92 (0.88–0.97)	0.0015
8–12 drinks/week	Yes	589/1601	(36.8)	0.89 (0.81–0.98)	0.021	0.90 (0.81–0.99)	0.034
>12 drinks/week	Yes	1138/2738	(41.6)	0.95 (0.86–1.04)	0.25	0.96 (0.87–1.05)	0.37
Clinical AIDS [§*]	No	6153/17844	(34.5)	1.71 (1.48–1.97)	<0.0001		
	Yes	6269/11956	(54.2)				

NC-AE medication use at visit was used as the dependent (outcome) variable. Logistic regression analysis with exchangeable within-woman correlation was performed on all observations (visits) for all individuals. Odds ratios are shown with and without adjusting for HIV-positive status. RDU= recreational drug use. OR= odds ratio. aOR= adjusted odds ratio. CI= confidence interval.

[♦] = No alcohol use (abstain) was used as the reference for the other alcohol use categories.

[§] = Visits at or subsequent to AIDS diagnosis.

[*] = Analysis conducted on HIV-infected individuals only.

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Table 4

NC-AE medication use as a predictor for HIV treatment outcomes

Outcome	NC-AE medication use	Outcome/visits	(%)	OR (95% CI)	*p*-value
Reported cART use	No	12441/17375	(71.6)	1.46 (1.35–1.57)	<0.0001
	Yes	9731/12422	(78.3)		
Reported adherence ≥95%*	No	9210/11185	(82.3)	1.03 (0.95–1.12)	0.45
	Yes	9072/10947	(82.9)		
Undetectable viral load§	No	8753/15998	(54.7)	1.12 (1.05–1.19)	0.0008
	Yes	6277/11350	(55.3)		

NC-AE medication use was used as the independent (predictor) variable for this analysis. Logistic regression analysis with exchangeable within-woman correlation was performed on all observations (visits) for all HIV-infected individuals. No NC-AE medication use was used as the reference.

* = reported adherence to cART therapy in six months preceding visit.

§ = both cART and non-CART visits included in the analysis.

OR= odds ratio. CI= confidence interval. cART= combination antiretroviral therapy.