Polypharmacy and Risk of Antiretroviral Drug Interactions Among the Aging HIV-Infected Population

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BACKGROUND: Among aging HIV-infected adults, polypharmacy and its consequences have not been well-described.

OBJECTIVE: To characterize the extent of polypharmacy and the risk of antiretroviral (ARV) drug interactions among persons of different ages.

DESIGN AND PARTICIPANTS: Cross-sectional analysis among patients within the HIV Outpatient Study (HOPS) cohort who were prescribed ARVs during 2006–2010.

MAIN MEASURES: We used the University of Liverpool HIV drug interactions database to identify ARV/non-ARV interactions with potential for clinical significance.

KEY RESULTS: Of 3,810 patients analyzed (median age 46 years, 34 % ≥ 50 years old) at midpoint of observation, 1,494 (39 %) patients were prescribed ≥ 5 non-ARV medications: 706 (54 %) of 1,312 patients ≥ 50 years old compared with 788 (32 %) of 2,498 patients < 50 years. During the five-year period, the number of patients who were prescribed at least one ARV/non-ARV combination that was contraindicated or had moderate or high evidence of interaction was 267 (7 %) and 1,267 (33 %), respectively. Variables independently associated with having been prescribed a contraindicated ARV/non-ARV combination included older age (adjusted odds ratio [aOR] per 10 years of age 1.17, 95 % CI 1.01–1.35), anxiety (aOR 1.78, 95 % CI 1.32–2.40), dyslipidemia (aOR 1.96, 95 % CI 1.28–2.99), higher daily non-ARV medication burden (aOR 1.13, 95 % CI 1.10–1.17), and having been prescribed a protease inhibitor (aOR 2.10, 95 % CI 1.59–2.76). Compared with patients < 50 years, older patients were more likely to have been prescribed an ARV/non-ARV combination that was contraindicated (unadjusted OR 1.44, 95 % CI 1.14–1.82), or had moderate or high evidence of interaction (unadjusted OR 1.29, 95 % CI 1.15–1.44).

CONCLUSIONS: A substantial percentage of patients were prescribed at least one ARV/non-ARV combination that was contraindicated or had potential for a clinically significant interaction. As HIV-infected patients age and experience multiple comorbidities, systematic reviews of current medications by providers may reduce risk of such exposures.

Received September 27, 2012
Revised February 5, 2013
Accepted March 20, 2013
Published online April 20, 2013

KEY WORDS: polypharmacy; drug interactions; HIV; aging.
J Gen Intern Med 28(10):1302–10
DOI: 10.1007/s11606-013-2449-6

INTRODUCTION

Combination antiretroviral (ARV) therapy has significantly decreased morbidity and mortality in the HIV-infected population.[1–4] With continued use of ARV therapy and maintenance of long-term adherence, HIV becomes a chronic and manageable condition.[2,5] As persons infected with HIV live longer, the percentage of older individuals in the HIV-infected population has increased. In the United States (US) in 2009, persons aged 50 years and older accounted for 33 % of all individuals living with HIV/AIDS, nearly double the 17 % reported for 2001.[6] It is estimated that by 2020, more than 50 % of persons living with HIV infection will be aged 50 years or older.[7]

Polypharmacy, defined as the concomitant use of multiple medications (e.g., customarily five or more medications), has been associated with increasing age[8,9] and with an increased risk of adverse drug reactions, increased hospitalizations, poor adherence, inappropriate drugs, falls and fractures, and drug–drug interactions.[10–15] The risk for drug–drug interactions may be particularly increased among the aging population of HIV-infected adults due to treatments for multiple comorbidities in this population[16–19] as well as the concomitant use of ARV therapy. Among the antiretroviral classes, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are major substrates as well as both inhibitors and inducers of the cytochrome P450 (CYP) enzyme system.[20] Introduction of low-dose ritonavir to "boost" bioavailability of most PIs has further increased risk for clinically significant drug interactions;[21] ritonavir is an extremely potent inhibitor of CYP 3A4 and 2D6, both of which metabolize nearly 70 % of all medications that undergo CYP450 metabolism.[22,23] PIs and NNRTIs can also affect activity of P-glycoprotein, a ubiquitous transport protein that prevents accumulation of toxins.[24]

Although polypharmacy and its impact on drug–drug interactions has been well-described in various studies from the general population,[13,14,25–33] there are limited data among the aging population of HIV-infected adults.[2,34–36] Therefore, we sought to examine the potential impact of polypharmacy on the risk of drug–drug interactions between ARVs and other medications (ARV/non-ARV interactions) in a US cohort of HIV-infected adults seen in the outpatient setting. In particular, we aimed to characterize the extent of polypharmacy, determine the types of medication classes prescribed and rate of prescribed ARV/non-ARV combinations with the potential for clinically significant interactions among persons of different ages, and identify risk factors for such exposures.

METHODS

The HIV Outpatient Study (HOPS)

The HOPS is an ongoing prospective observational cohort study of HIV-infected adults that has accrued data longitudinally since 1993. In this cross-sectional analysis, we included data from eight clinics (university-based, public, and private) participating in the HOPS after January 1, 2006, located in the following six cities: Chicago, IL; Denver, CO; Stony Brook, NY; Philadelphia, PA; Tampa, FL; and Washington, DC. Patient data, including demographic and social characteristics, symptoms, diagnoses, prescribed medications (including dose and duration), and laboratory values are abstracted from medical charts and entered by trained staff into a single database. These data are reviewed for quality and analyzed centrally. Data quality assurance measures include supervisory reviews of randomly selected charts to ascertain accuracy and completeness of abstracted data, and centralized checks of data files to resolve discrepancies in diagnosis and treatment start and stop dates, and in diagnosis codes versus descriptive text field information. Annually, the institutional review boards of the Centers for Disease Control and Prevention (Atlanta, GA), Cerner Corporation (Vienna, VA), and each local site have reviewed and approved the HOPS protocol and consents. The study protocol conforms to the guidelines of the US Department of Health and Human Services (DHHS) for the protection of human participants in research. The present analysis is based on the HOPS data set updated as of June 30, 2011.

Study Population

We performed cross-sectional analyses of patients who were classified as active (i.e., having attended at least two medical visits) in the HOPS from January 1, 2006 to December 31, 2010. For our analysis, active patients were selected who had a CD4+ T-lymphocyte (CD4) count and HIV RNA viral load (VL) recorded within 6 months before or during the 5-year study period, and who had taken ARV therapy for > 2 weeks during the study period. Observation period started on January 1, 2006 or the first HOPS visit thereafter (referred to as the "baseline" date). It extended to the earlier of death date, last HOPS visit plus six months or December 31, 2010, allowing for up to 5 years of observation for each patient.

Outcome Variables

We used the comprehensive University of Liverpool HIV drug interactions database (www.hiv-druginteractions.org), which aggregates published findings chiefly from European and North American studies to classify a medication as contraindicated or as having moderate or high evidence of interaction with a concurrently prescribed ARV. Non-ARV drug classes and categories were adapted from this database. We considered only combinations of prescribed ARV medications with prescribed non-ARV medication (termed from here on "ARV/non-ARV combinations") where both drugs had been prescribed concomitantly for > 1 day.

Independent Variables: Definitions for Analysis

Values for baseline characteristics were values assessed during the preceding 6 months that were closest to the baseline date. The presence or absence of a diagnosis at baseline was based on diagnoses made before the baseline date and within 6 months thereafter. Insurance status was classified as private, public or none (i.e., uninsured). Illicit substances included amphetamines, cocaine, and heroin. "Poly-substance abuse" and "alcohol abuse" were determined from documentation of such in the medical chart notes. The category "other mental illness" included psychosis, schizophrenia, bipolar disorder, mania, or chronic mental illness. In addition to Hodgkin lymphoma and leukemia, cancers at the following anatomic sites were defined as non-AIDS-defining: skin, liver, lung, bone, brain (excluding primary CNS lymphoma), breast, ovarian, prostate, testes, thyroid gland, esophagus, kidney, pancreas, stomach, small bowel, colon, and anorectum. Although polypharmacy is typically defined as concomitant use of five or more medications,[37] in the case of HIV-infected patients who are frequently prescribed three or more medications (ARVs) to treat one condition (HIV infection), we also describe total and non-ARV medication burden so that alternative cut-offs for characterizing polypharmacy could be considered.

Statistical Analyses

We assessed the percentage of patients within the 5-year study period who were prescribed ≥ 1 ARV/non-ARV combination that was contraindicated or had moderate or high evidence of interaction. We compared patient characteristics between groups using chi-square tests for categorical variables and Wilcoxon or Kruskal-Wallis tests for continuous variables. We used Yates corrected chi-square tests to compare percentages of patients prescribed specific medication classes and frequencies of ARV/non-ARV combinations with clinically significant interactions among patients < 50 vs. ≥ 50 years old at the midpoint of observation for each patient. We used multivariable logistic regression to obtain adjusted odds ratios (aORs) with associated 95 % confidence intervals (CIs) and assess factors independently associated with having been prescribed ARV/non-ARV combinations that were either contraindicated or had moderate or high evidence of interaction. In all modeling, variables with a univariate significance level (p value) < 0.05 were initially included in multivariable analyses. We constructed final multivariable models using backward manual selection procedures, retaining only those variables for which the significance level was < 0.05. Descriptive data summaries, and univariate and multivariable logistic regression analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Yates corrected chi-square tests were performed using StatCalc (EpiInfo 2002 revision 2; Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Patient Baseline Characteristics

Among the 4,145 active patients with at least two visits in the HOPS anytime from January 1, 2006 to December 31, 2010, we excluded 335 for the following reasons (applied hierarchically): 268 were prescribed antiretroviral therapy for < 2 weeks during follow-up, 46 had no recorded CD4 count, and 21 had no recorded HIV VL.

Demographic and clinical characteristics of the 3,810 patients in our analytic cohort stratified by age at baseline are shown in Table 1. Among these patients (median age, 44 years), 1,189 (31 %) were < 40 years old, 1,615 (42 %) were 40–49 years old, and 1,006 (26 %) were ≥ 50 years old. Overall, 3,001 (79 %) were male, 1,800 (47 %) were non-white race or Hispanic ethnicity and 2,158 (57 %) had private insurance. The median baseline CD4 count was 432 cells/μL (interquartile range [IQR], 255–640 cells/μL) and 2,169 (57 %) patients had a prior AIDS diagnosis.

As expected, the percentage of patients diagnosed with dyslipidemia, hypertension, cardiovascular disease, diabetes, and non-AIDS-defining cancers increased with age (Table 1). Greater percentages of older persons compared with younger persons also had injection drug use as their risk factor for HIV transmission (3.4 % < 40 years old, 8.8 % 40–49 years old, and 13 % ≥ 50 years old), were co-infected with hepatitis B or C virus (9.5 % < 40 years old, 20 % 40–49 years old, and 25 % ≥ 50 years old), and were current or former tobacco smokers (39 % < 40 years old, 43 % 40–49 years old, and 44 % ≥ 50 years old). Older patients had a higher median daily non-ARV medication burden: two (IQR 1–4) for age < 40 years, three (IQR 1–6) for age 40–49 years, and four (IQR 2–7) for age 50 years (P <0.001).

Frequency of Prescriptions of ARV/non-ARV Combinations with Potential for Clinically Significant Interactions

Among the 3,810 patients analyzed during the 5-year observation period, 267 (7 %) were prescribed at least one contraindicated ARV/non-ARV combination. Average duration of prescribed contraindicated combinations per year of observation was 82 days. In addition, 1,267 (33 %) patients were prescribed at least one ARV/non-ARV combination with moderate or high evidence of interaction. Average duration of prescribed interacting combinations per year of observation was 71 days.

Among the 267 patients prescribed one or more contraindicated ARV/non-ARV combinations, 163 (61 %) were prescribed a proton pump inhibitor (PPI) together with either atazanavir or nelfinavir, 50 (19 %) were prescribed a contraindicated statin (simvastatin or lovastatin) together with a PI, and 42 (16 %) were prescribed a contraindicated benzodiazepine (alprazolam, triazolam, diazepam, clorazepate, and flurazepam) together with a PI (Fig. 1).

Among the 1,267 patients prescribed at least one ARV/non-ARV combination with moderate or high evidence of interaction, the most commonly prescribed medications were H_2 antagonists and PPIs together with PIs (25 %), erectile dysfunction agents together with PIs and NNRTIs (22 %), and the antidepressants, bupropion, sertraline, and paroxetine together with PIs and NNRTIs and lithium together with atazanavir (19 %).

Factors Associated with Prescription of ARV/non-ARV Combinations with Potential for Clinically Significant Interactions

In multivariable logistic regression analyses, baseline variables independently associated with increased odds of

Table 1. Demographic and Clinical Characteristics of the 3,810 Patients at Baseline, Stratified by Age, the HIV Outpatient Study, 2006–2010

Baseline Characteristic*	Age < 40 years (*n*=1,189)	Age 40–49 years (*n*=1,615)	Age ≥ 50 years (*n*=1,006)	P value†
Age, years: median (IQR‡)	34 (29–37)	44 (42–47)	54 (52–58)	< 0.001
Male sex, n (%)	861 (72.4)	1,304 (80.7)	836 (83.1)	< 0.001
Race and ethnicity, n (%)				< 0.001
White, non-Hispanic	513 (43.2)	901 (55.8)	596 (59.2)	
Black, non-Hispanic	453 (38.1)	475 (29.4)	286 (28.4)	
Hispanic	174 (14.6)	181 (11.2)	97 (9.6)	
Other	49 (4.1)	58 (3.6)	27 (2.7)	
Year of HOPS entry, n (%)				< 0.001
2005 or earlier	724 (60.9)	1,234 (76.4)	805 (80.0)	
2006 or later	465 (39.1)	381 (23.6)	201 (20.0)	
Years observed, median (IQR)	4.3 (2.3–5.0)	5.0 (2.8–5.0)	5.0 (2.6–5.0)	< 0.001
Total person-years of observation	4,308	6,306	3,895	0.19
Primary insurance type, n (%)				0.05
Private	666 (56.0)	942 (58.4)	550 (54.7)	
Public	408 (34.3)	544 (33.7)	383 (38.1)	
None	115 (9.7)	127 (7.9)	73 (7.3)	
HIV risk, n (%)				< 0.001
MSM	691 (58.1)	959 (59.4)	567 (56.4)	
Heterosexual	372 (31.3)	397 (24.6)	233 (23.2)	
IDU	40 (3.4)	142 (8.8)	131 (13.0)	
Other/unknown	86 (7.2)	117 (7.2)	75 (7.5)	
Prior AIDS diagnosis, n (%)	538 (45.3)	978 (60.6)	653 (64.9)	< 0.001
Current/prior tobacco use, n (%)	461 (38.8)	690 (42.7)	446 (44.3)	0.02
Illicit substance§ or alcohol abuse, n (%)	77 (6.5)	156 (9.7)	78 (7.8)	0.01
Depression, n (%)	399 (33.6)	633 (39.2)	366 (36.4)	0.01
Anxiety, n (%)	155 (13.0)	265 (16.4)	167 (16.6)	0.02
Insomnia, n (%)	162 (13.6)	258 (16.0)	186 (18.5)	0.008
Other mental illness‖, n (%)	79 (6.6)	122 (7.6)	59 (5.9)	0.24
Cancer¶, n (%)	26 (2.2)	85 (5.3)	104 (10.3)	< 0.001
Dyslipidemia, n (%)	702 (59.0)	1,246 (77.2)	820 (81.5)	< 0.001
Hypertension, n (%)	212 (17.8)	489 (30.3)	513 (51.0)	< 0.001
Cardiovascular disease, n (%)	78 (6.6)	172 (10.7)	218 (21.7)	< 0.001
Diabetes, n (%)	83 (7.0)	193 (12.0)	249 (24.8)	< 0.001
Hepatitis B or C, n (%)	113 (9.5)	321 (19.9)	250 (24.9)	< 0.001
Nadir CD4+ cell count < 200 cells/mm^3, n (%)	515 (43.3)	860 (53.3)	545 (54.2)	< 0.001
Nadir CD4+ cell count, cells/mm^3, median (IQR)	236 (74–351)	181 (59–320)	182 (67–325)	< 0.001
CD4+ cell count, cells/mm^3, median (IQR)	419 (243–603)	432 (253–655)	444 (270–661)	0.01
CD4+ cell count category, cells/mm^3				0.03
< 200	241 (20.3)	304 (18.8)	168 (16.7)	
200–349	219 (18.4)	321 (19.9)	202 (20.1)	
350–499	279 (23.5)	315 (19.5)	203 (20.2)	
500+	450 (37.9)	675 (41.8)	432 (43.0)	
HIV RNA viral load, $\log_{10}$ copies/mL, median (IQR)	2.6 (1.4–4.5)	1.5 (1.4–4.0)	1.4 (1.4–2.8)	< 0.001
Viral load < 400 copies/mL, n (%)	593 (49.9)	1,029 (63.7)	741 (73.7)	< 0.001
Daily number of non-ARV prescription medications prescribed, median (IQR)	2 (1–4)	3 (1–6)	4 (2–7)	< 0.001
Daily number of ARV medications prescribed, median (IQR)	3 (0–3)	3 (1–3)	3 (3–3)	< 0.001
Total daily number of medications prescribed, median (IQR)	4 (2–6)	5 (3–8)	7 (4–10)	< 0.001
ARV treatment status				< 0.001
ARV-naïve, n (%)	321 (27.0)	222 (13.8)	114 (11.3)	
ARV-experienced, currently not prescribed ARVs, n (%)	130 (10.9)	161 (10.0)	78 (7.8)	
ARV-experienced, currently prescribed ARVs, n (%)	738 (62.1)	1,232 (76.3)	814 (80.9)	
Time prescribed ARVs during follow-up, n (%)				< 0.001
< 75 %	179 (15.1)	208 (12.9)	76 (7.6)	
75–99 %	286 (24.2)	557 (34.6)	345 (34.3)	
100 %	719 (60.7)	845 (52.5)	584 (58.1)	
ARV regimen type, n (%)				0.17
PI-containing	369 (31.0)	619 (38.3)	411 (40.9)	
NNRTI-containing	306 (25.7)	468 (29.0)	301 (29.9)	
PI and NNRTI-containing	24 (2.0)	61 (3.8)	49 (4.9)	
Triple NRTI	22 (1.9)	48 (3.0)	30 (3.0)	
Non-HAART#	11 (0.9)	26 (1.6)	19 (1.9)	
Integrase inhibitor	6 (0.5)	5 (0.3)	2 (0.2)	
Fusion inhibitor	0 (0.0)	3 (0.2)	1 (0.1)	
Other ARV agent**	0 (0.0)	2 (0.1)	1 (0.1)	

**Characteristics and diagnoses were applied as follows: insurance status at closest visit to baseline date; any diagnoses up to 6 months after baseline date; nadir CD4 at any time before or during follow-up period; CD4 cell count at closest visit to baseline date; viral load at closest visit to baseline date; ARV experience up to and including beginning of baseline date; daily number of medications taken at closest visit to baseline date*

†Comparisons made across three age groups

‡IQR interquartile range, MSM men who have sex with men, IDU injection drug use, ARV antiretroviral, PI protease inhibitor, NNRTI non-nucleoside reverse transcriptase inhibitor, NRTI nucleoside/nucleotide reverse transcriptase inhibitor, HAART highly active antiretroviral therapy

§Illicit substances includes the following entries: amphetamines, cocaine, heroin, poly-substance abuse

‖Other mental illness includes the following diagnosis entries: psychosis/schizophrenia, bipolar disorder, mania, chronic mental illness

¶Cancers are non-AIDS-defining: Hodgkin, skin, liver, lung, bone, brain, breast, ovarian, prostate, testicular, anal/rectal, colon, thyroid, esophageal, renal, pancreatic, leukemia, stomach/GI, other

#HAART defined as three or more ARVs from two different classes

***Two dual NRTI regimens, one not specified*

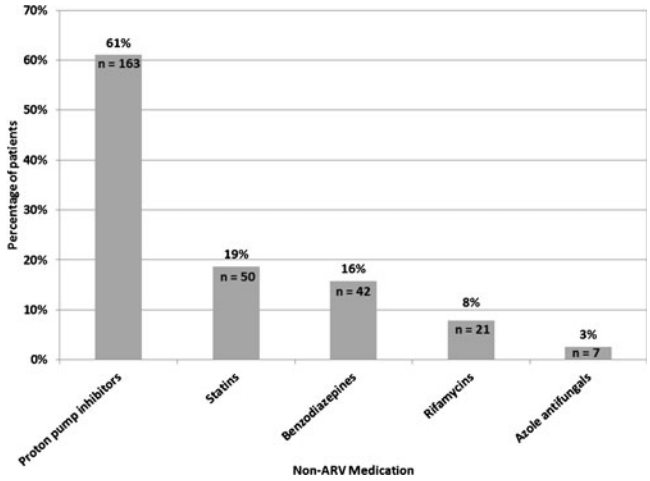

Figure 1. Non-ARVs prescribed among patients prescribed contraindicated ARV/non-ARV combinations (N=267)*, by class. *Some patients were prescribed more than one contraindicated non-ARV medication together with an ARV, or different contraindicated combinations at different times during the observation.

being prescribed a contraindicated ARV/non-ARV combination included older age, anxiety, dyslipidemia, higher daily non-ARV medication burden, and having been prescribed a PI (Table 2). Baseline variables independently associated with higher odds of being prescribed an ARV/non-ARV combination with moderate or high evidence of interaction (but not contraindicated) are also shown in this table. Higher nadir CD4 cell count was associated with lower odds of having been prescribed an ARV/non-ARV combination with moderate or high evidence of interaction (Table 2).

Frequency of Prescribed Total and Non-ARV Medications and Differences in Prescribed Specific Medication Classes Stratified by Age

Figures 2a and 2b show the total number of medications and the number of non-ARV medications, respectively, prescribed at midpoint of observation for each patient, stratified by age. Of 3,810 patients analyzed (median age 46 years), 2,319 (61 %) patients were prescribed ≥ 5 medications (including ARVs): 969 (74 %) of 1,312 patients ≥ 50 years old (median age 55 years) compared with 1,350 (54 %) of 2,498 patients < 50 years (median age 42 years) (Fig. 2a). Overall, 1,494 (39 %) patients were prescribed ≥ 5 non-ARV medications: 706 (54 %) of 1,312 patients ≥ 50 years old compared with 788 (32 %) of 2,498 patients < 50 years (Fig. 2b).

Figure 3 shows the percentage of patients prescribed specific medication classes at the midpoint of observation for each patient, stratified by age at the time of classification. During the 5-year period, compared with patients < 50 years, older patients were more likely to have been prescribed an ARV/non-ARV combination that was contraindicated (2.86 versus 1.98 per 100 person-years, unadjusted OR 1.44, 95 % CI 1.14–1.82) or had moderate or high evidence of interaction (15.6 vs. 12.1 per 100 person-years, unadjusted OR 1.29, 95 % CI 1.15–1.44).

DISCUSSION

Polypharmacy has been shown to increase the risk of adverse drug reactions and geriatric syndromes such as

Table 2. Univariate and Multivariable Logistic Regression of Factors Associated with Prescription of ARV/non-ARV Combinations, the HIV Outpatient Study, 2006–2010 (*N*=3,810)

Baseline Characteristic	Contraindicated ARV/non-ARV combinations		ARV/non-ARV combinations with moderate or high evidence of interaction, but not contraindicated	
	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
Age per 10 years	1.49 (1.31–1.69)	1.17 (1.01–1.35)	1.36 (1.26–1.45)	1.13 (1.04–1.23)
Non-Hispanic white race/ethnicity	1.59 (1.23–2.06)	–	0.98 (0.85–1.12)	–
Year of HOPS entry ≤ 2005	2.74 (1.90–3.96)	–	1.84 (1.57–2.17)	1.26 (1.04–1.52)
Private insurance	0.86 (0.67–1.10)	–	0.72 (0.63–0.82)	–
MSM HIV risk	1.14 (0.88–1.47)	–	0.80 (0.69–0.91)	–
Prior AIDS diagnosis	1.40 (1.08–1.82)	–	1.83 (1.59–2.10)	–
Current or prior smoker	1.39 (1.08–1.78)	–	1.43 (1.25–1.64)	1.16 (1.00–1.35)
Illicit substance* or alcohol abuse	0.61 (0.35–1.05)	–	1.93 (1.53–2.44)	1.46 (1.13–1.88)
Depression	1.62 (1.26–2.08)	–	2.03 (1.77–2.33)	1.47 (1.26–1.71)
Anxiety	2.46 (1.86–3.26)	1.78 (1.32–2.40)	1.68 (1.40–2.01)	–
Other mental illness†	1.18 (0.74–1.88)	–	1.47 (1.13–1.89)	–
Cancer	1.23 (0.75–2.02)	–	1.36 (1.03–1.81)	–
Dyslipidemia	3.57 (2.38–5.35)	1.96 (1.28–2.99)	1.88 (1.60–2.21)	1.24 (1.03–1.49)
Hypertension	2.02 (1.57–2.59)	–	1.82 (1.58–2.09)	–
Cardiovascular disease	1.82 (1.32–2.50)	–	1.81 (1.49–2.21)	–
Diabetes	2.06 (1.53–2.78)	–	1.57 (1.30–1.90)	–
Hepatitis B or C	1.26 (0.93–1.71)	–	1.60 (1.35–1.89)	–
CD4+ cell count per 100 cells (cells/mm^3)	1.02 (0.98–1.06)	–	0.97 (0.95–0.99)	–
Nadir CD4+ cell count per 100 cells (cells/mm^3)	0.91 (0.85–0.98)	–	0.85 (0.81–0.88)	0.94 (0.90–0.98)
HIV RNA viral load, $\log_{10}$ copies/mL	0.86 (0.79–0.95)	–	1.02 (0.97–1.06)	1.12 (1.07–1.19)
Daily non-ARV medication burden	1.18 (1.15–1.21)	1.13 (1.10–1.17)	1.19 (1.17–1.21)	1.13 (1.11–1.16)
Prescription of a PI-containing ARV regimen	3.12 (2.40–4.05)	2.10 (1.59–2.76)	2.17 (1.90–2.49)	1.54 (1.32–1.80)

**Illicit substances includes the following entries: amphetamines, cocaine, heroin, poly-substance abuse*
†*Other mental illness includes the following diagnosis entries: psychosis/schizophrenia, bipolar disorder, mania, chronic mental illness*

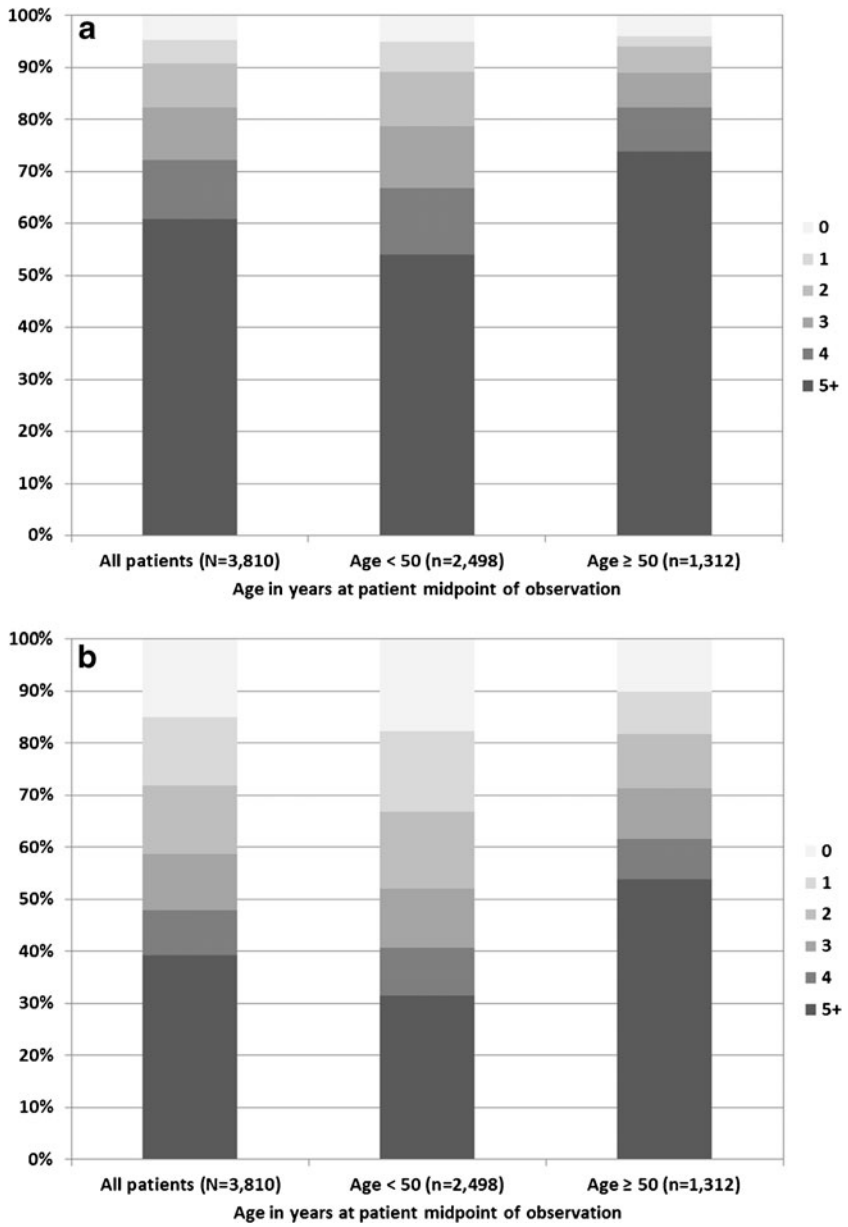

Figure 2. a Number of total medications (including ARVs) prescribed, overall and by age group, the HIV Outpatient Study, 2006–2010 (*N*=3,810). b Number of non-ARV medications prescribed, overall and by age group, the HIV Outpatient Study, 2006–2010 (*N*=3,810).

cognitive impairment, urinary incontinence, and falls.[38] In this cross-sectional analysis spanning a 5-year period, we found that a greater number of daily non-ARV medication can also increase the risk of ARV/non-ARV combinations with potential for clinically significant interactions for HIV-infected persons, particularly those ≥ 50 years old. With increasing age, comorbidities such as cardiovascular disease, hyperlipidemia, diabetes, non-AIDS-defining cancers, and declines in renal and hepatic function become highly prevalent among HIV-infected patients.[16–19] A Southern Alberta Cohort Study examining the total daily pill burden (TDPB) among HIV-infected patients over a period of 20 years found that there was a higher TDPB among older patients due to increases in non-ARV drugs required for managing comorbidities.[2] Consistent with this study, a greater proportion of older patients in the HOPS were prescribed ≥ 5 non-ARV medications as well as ≥ 5 total medications (including ARVs) compared with those < 50 years old. In addition, patients ≥ 50 years old were more likely to have been prescribed an ARV/non-ARV combination that was contraindicated or had moderate or high evidence of interaction.

Among this aging, HIV-infected cohort (median age, 44 years), 7 % of patients were prescribed at least one ARV/non-ARV combination that was contraindicated and 33 % were prescribed a combination that had moderate or high evidence of interaction. Prescription of contraindicated ARV/non-ARV combinations predominantly involved the use of PPIs, statins (simvastatin and lovastatin) and benzodiazepines, agents frequently prescribed in this cohort

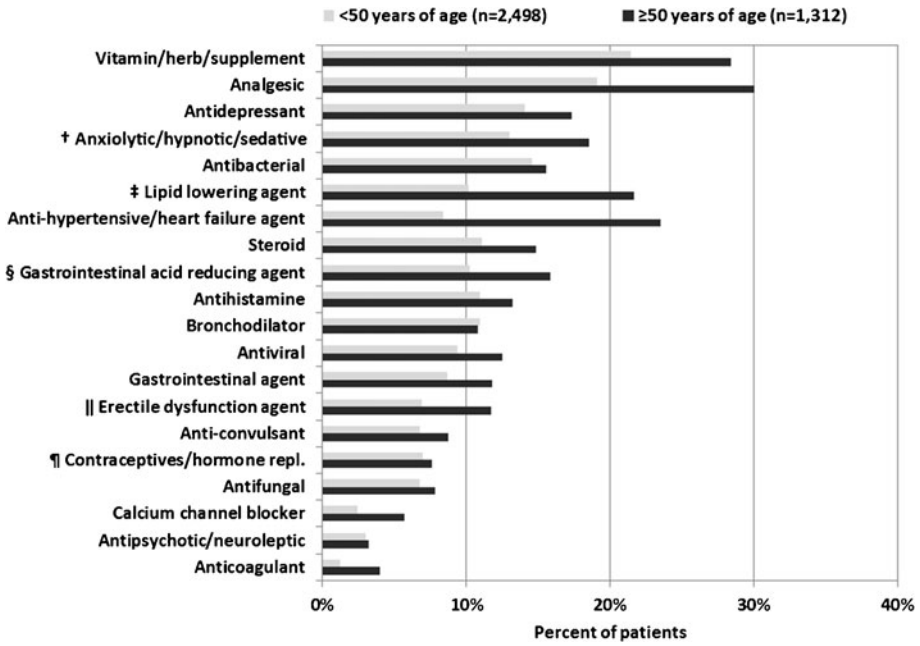

Figure 3. Prescribed non-ARV medications by class and age, the HIV Outpatient Study, 2006–2010 (N=3,810)* . *Age group and medication use defined/determined at midpoint of patient observation. †Benzodiazepines ‡Statins §Proton Pump Inhibitors ‖Among males ¶Among females

and commonly used for the treatment of comorbidities among older patients. For example, 73 % of patients in our study had a baseline diagnosis of dyslipidemia, for which statins are first-line pharmacological agents.[39] Co-administration of simvastatin and lovastatin with protease inhibitors may significantly increase serum levels of the statin, resulting in potential myopathy, including rhabdomyolysis.[40,41]

In contrast to the results of our study, the Swiss HIV Cohort Study found that only 2 % of their patients had been prescribed contraindicated ARV/non-ARV combinations, which largely involved midazolam,[35] while 59 % had been prescribed ARV/non-ARV combinations that were not contraindicated, yet had interactions requiring potential dose adjustment and/or close monitoring. The differences between our observations and those of the Swiss HIV Cohort Study scientists may be explained at least in part by their use of a customized version of the Liverpool database, use of different definitions for important but not contraindicated interactions, and their review of all interactions by two pharmacists.

According to the US DHHS guidelines on the use of antiretroviral agents in adults and adolescents, providers should thoroughly review patients' current medications in order to design an ARV regimen that minimizes undesirable drug interactions[35,42] and utilize medication therapy management (MTM) services for patients with complex medical histories. ARV regimen modification, dose adjustment, and substitution of certain non-ARV or ARV drugs may be required in some patients. Significant drug interactions with different ARV agents and suggested recommendations on contraindications, dose modifications, and alternative agents can be found in the DHHS guidelines as well as online drug interactions databases, such as the University of Liverpool HIV drug interactions database. The addition of MTM services (CPT codes 99605-99607 for reimbursement) that include pharmacists can help ensure that a thorough evaluation for potential drug interactions takes place, especially for patients prescribed multiple co-medications with their ARV regimens.[43] Finally, electronic medical record systems that provide information on the clinical relevance of drug–drug interactions, availability of therapeutic alternatives, and monitoring parameters or management options may decrease the risk of toxicities or therapeutic failure.[44]

We acknowledge the challenges providers face following these recommendations when caring for patients who frequently experience multiple chronic comorbidities.[7,35] Our objective is to focus attention on the real burden of polypharmacy and clinically significant drug interactions among the HIV population. There are many circumstances in which co-prescribing of medications with the potential for drug interactions may be unavoidable, especially if patients have limited therapeutic options for treatment of their HIV infection or comorbidities. Drug interactions are not always clinically significant and providers may have been well aware of these interactions and monitored patients closely or made dosage adjustments.

There are several limitations to our study. First, we analyzed medications that were prescribed concurrently but cannot ascertain if they were actually taken by the patient as prescribed. Second, recommendations on ARV/non-ARV combinations according to the University of Liverpool database may differ from US labeling or guidelines, since the University of Liverpool database considers recommendations from both US and European labeling. Therefore, estimates of prescription of contraindicated ARV/non-ARV combinations in our cohort may be slightly lower if based solely on US labeling or guidelines. Third, in evaluating the medication burden, we did

not systematically collect and could not account for use of over-the-counter drugs or herbal medications, some of which have significant potential for interaction with ARVs. Fourth, we also did not examine interactions between multiple non-ARV agents that patients may be prescribed, only interactions between ARVs and non-ARVs; therefore, our estimates may be conservative in terms of the total burden of drug–drug interactions. Finally, we did not examine the contribution of the many different ARV/non-ARV interactions to major clinical outcomes, such as virologic failure, end-organ injury or treatment discontinuation, because our medical record-based observational study of patients in routine HIV care is not well powered or adequately controlled for this purpose.

In conclusion, a substantial minority of patients in our large multi-site US HIV cohort was prescribed ARV/non-ARV combinations with the potential for clinically significant interactions, and the risk for exposure to such combinations increased with age. Reasons for this finding include the overall increasing use of co-medications and the high prevalence of comorbidities among older patients for which treatments often interact with ARVs. Providers should thoroughly review and adjust patients' current medications in order to minimize the potential drug interactions with their ARV regimens and consider medical therapy management monitoring for patients with multiple comorbidities.

Acknowledgements:
Disclaimer: *The findings and conclusions of this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.*

Funders: *The Centers for Disease Control and Prevention (CDC) supported the HOPS data collection through a contract with the Cerner Corporation. The co-authors from the CDC participated in the design of the study and the analysis and interpretation of the data and approved the final version of the manuscript.*

Prior presentations: *This manuscript was presented at the XIX International AIDS Conference in Washington DC, USA on July 24th, 2012.*

Conflict of Interest: *The authors state that they have no financial disclosures or conflicts of interest to report.*

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