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Nonantiretroviral polypharmacy and adverse health outcomes among HIV-infected and uninfected individuals

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Background: HIV-positive individuals (HIV+) on antiretrovirals commonly take enough other medications to cross a threshold for polypharmacy but little is known about associated outcomes. We asked whether non-antiretroviral polypharmacy is associated with hospitalization and mortality and whether associations differ by HIV status.

Methods: Data on HIV+ and uninfected individuals in the US Veterans Affairs Healthcare System were analyzed. Eligible HIV+ were on antiretrovirals with suppressed HIV-1 RNA and uninfected individuals received at least one medication. We calculated average non-antiretroviral medication count for fiscal year 2009. As there is no established threshold for non-antiretroviral polypharmacy, we considered more than two and at least five medications. We followed for hospitalization and mortality (fiscal year 2010–2015), adjusting for age, sex, race/ethnicity and VACS Index.

Results: Among 9473 HIV+ and 39 812 uninfected individuals respectively, non-antiretroviral polypharmacy was common (>2: 67, 71%; ≥5: 34, 39%). VACS Index discriminated risk of hospitalization (c-statistic: 0.62, 0.60) and mortality (c-statistic: 0.72, 0.70) similarly in both groups. After adjustment, more than two (hazard ratio 1.51, 95% CI 1.46–1.55) and at least five non-antiretrovirals (hazard ratio 1.52, 95% CI 1.49–1.56) were associated with hospitalization with no interaction by HIV status. Risk of mortality associated with more than two non-antiretrovirals interacted with HIV status ($P = 0.002$), but not for at least five (adjusted hazard ratio 1.43, 95% CI 1.36–1.50). For both groups and both outcomes, average medication count demonstrated an independent, dose response, association.

Conclusion: Neither severity of illness nor demographics explain a dose response, association of non-antiretroviral polypharmacy with adverse health outcomes among HIV+ and uninfected individuals.

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Introduction

In observational studies of the general population, the use of more than five concurrent medications constitutes polypharmacy [1]. In this group, polypharmacy is widespread and associated with adverse drug events, inappropriate prescribing, falls, cognitive compromise, hospitalization, and mortality [2,3]. Combination antiretroviral treatment for HIV infection with three or more medications dramatically improves morbidity and extends survival but requires life-long treatment. Yet, antiretrovirals are known to have many drug–drug interactions with commonly co-prescribed medications [4,5]. If two or more non-antiretroviral medications are added, HIV-positive individuals (HIV+) would conventionally cross the threshold for polypharmacy [6]. Yet, no group has established a threshold for non-antiretroviral polypharmacy among HIV+ based on associations with hospitalization or mortality or compared associations with demographically similar uninfected individuals. Instead, studies characterizing non-antiretroviral polypharmacy in HIV+ have considered only potentially inappropriate medications because of drug–drug interactions or side effects [4,5,7–10].

Of special note, non-antiretroviral medications are prescribed to treat comorbid health conditions, as prophylaxis, or to treat adverse effects of antiretrovirals. Severity of illness because of comorbid conditions, not polypharmacy, may explain observed associations (confounding by indication) [11]. Although only a randomized trial can completely address this issue, adjusting for severity of illness using an accurate and validated prognostic index can help. However, few studies in the general population and no study among HIV+, have adjusted for severity of illness. In the general population, the studies that have adjusted for severity of illness have used self-reported functional status, health status, or comorbid conditions [11,12]. Such measures are often based on self-report or administrative diagnostic codes and provide limited discrimination of mortality [13–15]. No prior study associating polypharmacy with health outcomes, among those with or without HIV infection, has used a well validated, highly discriminating, index to comprehensively adjust for severity of illness.

On the basis of routine clinical laboratory data, the Veterans Aging Cohort Study (VACS) Index has been widely validated as a highly discriminating measure of severity of illness [16,17]. It accurately and reproducibly predicts all-cause mortality among those with and without HIV infection and is associated with hospitalization [18–20]. In this study, we compare nonantiretroviral polypharmacy, considering both more than two and at least five thresholds, between HIV+and demographically matched uninfected patients to determine: associated unadjusted and adjusted risk of hospitalization and mortality, whether risks differ by HIV status, and if a dose–response association exists between the number of non-antiretroviral medications and risk of hospitalization or mortality.

Methods

Study overview

We conducted a prospective analysis of the VACS described previously [21]. Briefly, VACS is a cohort of HIV+and uninfected individuals matched 1 : 2 on age, sex, race/ethnicity, and site of care identified from the United States Veterans Health Administration (VA) administrative data. Baseline was established in fiscal year 2009 (1 October 2008 to 30 September 2009). Data were obtained from the VA corporate data warehouse and included demographic characteristics, hospital and outpatient diagnoses [recorded using International Classification of Diseases, Ninth Revision (ICD-9) codes], laboratory results, and dispensed medications from the Pharmacy Benefits Management (PBM) Program. United States Medicare claims data were available for veterans also enrolled in this program and were merged with the VACS data. Patients were followed through September 2015.

Study population

We included HIV+ individuals receiving ART and uninfected individuals who were receiving at least one prescription medication from the VA in fiscal year 2009. HIV+ individuals were considered to be on ART if they were prescribed three or more antiretroviral agents, excluding low-dose ritonavir. We required uninfected individuals to be on at least one VA dispensed medication to insure that they were obtaining medications from the VA. Among patients alive at the end of fiscal year 2009, we excluded patients who had any cancer diagnosis except nonepithelial skin cancer ($n = 1874$) as their severity of illness may not be adequately reflected in the VACS Index; ambiguous HIV status ($n = 99$) to make a clear comparison between HIV+ and uninfected individuals; HIV+ individuals who were not virally suppressed (>400 HIV-1 RNA copies/ml) in the last 6 months of baseline fiscal year 2009 ($n = 9018$) – we sought to study polypharmacy among those on successful ART; 4) no VACS index score ($n = 4085$); and on more than 15 medications to eliminate highly leveraged observations ($n = 534$, 1% of the analytic sample).

Nonantiretroviral medication count and polypharmacy

We determined receipt of all outpatient preparations (i.e. oral, inhaled, or injectable) of medications dispensed through the VA using prescription pharmacy fill/refill data [21]. We excluded prescriptions classified as diagnostic supplies (e.g. glucose test strips); emollients; eye washes and lubricants; soaps, shampoos and soap-free cleaners; mouthwashes; sun protectants and screens;

irrigation solutions; ceruminolytics; deodorants and antiperspirants; and contact lens solutions from analyses. Our analysis was restricted to medications, which were filled on a chronic basis, defined as at least 90 consecutive days allowing for a 30-day refill window, consistent with previous definitions [22].

Days of medication receipt were calculated based on prescription information, assuming the prescription was taken as directed. Patients may have started a medication before fiscal year 2009 or continued them after fiscal year 2009; we captured only days supplied within fiscal year 2009. Medications were categorized according to VA class. We calculated the mean number of unique non-antiretroviral long-term medications received by each patient during fiscal year 2009 by summing the number of days supplied for each medication and dividing the total by 365 days. Each component of co-formulated medications was counted separately.

Adverse health outcomes

Hospitalization was identified from the VA (including fee-based) and Center for Medicare and Medicaid Services (CMS). All-cause mortality was obtained from the VA Vital Status File, which includes data from inpatient records, the VA Beneficiary Identification Records Locator Subsystem (BIRLS), Social Security Administration, and CMS. Excellent reliability and validity of the Vital Status File has been established by comparison with the National Death Registry [23]. We conducted surveillance for hospitalization and mortality; time to event was calculated from the start of fiscal year 2010 to the date of first event or censored at the end of fiscal year 2015.

Covariates

Demographic variables included age, race/ethnicity, and sex. Diabetes mellitus status was determined based on laboratory and pharmacy data [24]. BMI and blood pressure (uncontrolled hypertension) were obtained from clinic visit records. Controlled hypertension was based on a normal blood pressure and receipt of an antihypertensive. Hepatitis C virus (HCV) status was considered positive if a patient had a positive HCV antibody test or HCV RNA or ICD-9 codes for HCV infection. We determined the presence of other comorbid medical and psychiatric diseases by requiring at least one inpatient or two outpatient ICD-9 codes [25].

We used the VACS Index to adjust for disease severity [16–20]. The VACS Index is a physiologic score predicting risk of all-cause mortality initially developed among HIV+ individuals that integrates data on age; HIV biomarkers (HIV-1 RNA viral load; CD4 cell count); and non-HIV biomarkers (hemoglobin, hepatitis C; FIB-4 to assess liver function, and estimated glomerular filtration rate to assess renal function). It has also been validated in uninfected individuals [20]. Potential scores range from 0 to 164, with higher scores being associated with a greater risk of mortality. A five-point increase in VACS Index score is associated with a 20% increase in 5-year mortality risk (e.g. hazard ratio of 1.2). Scores were determined using laboratory values closest to the end of fiscal year 2009.

Analyses

In bivariate analyses, we evaluated characteristics of HIV+ and uninfected individuals associated with non-antiretroviral polypharmacy using a chi-square test and calculating odds ratios for more than two and at least five non-antiretroviral polypharmacy. We used Cox proportional hazard models to determine the association between non-antiretroviral medication count (and >2 and ≥ 5 thresholds for non-antiretroviral polypharmacy), hospitalization, and mortality adjusted for disease severity (as measured by the VACS Index) and demographic factors. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Role of the funding source

The funding source played no role in this analysis.

Results

Sample characteristics

During fiscal year 2009 (baseline), 9473 HIV+ were on antiretrovirals with suppressed HIV-1 RNA and 39 812 uninfected individuals were receiving at least one medication from VA pharmacy. Overall, the sample was predominantly 50–64 years of age (Table 1, 64, 64%), racially and ethnically diverse (41% white, 46% black, 9% Hispanic), predominantly men (98%) and demographically similar by HIV status. Both HIV+ and uninfected were actively engaged in care (mean visits/year: HIV+ 2.1, uninfected 1.9). Among HIV+ individuals, median CD4 count was 515 (IQR 347, 720). By design, all HIV+ individuals were on antiretrovirals (60% protease inhibitor-based, 40% nonnucleoside reverse transcriptase inhibitors, and $<0.1\%$ on an Integrase inhibitor) and had HIV-1 RNA 400 copies/ml or less.

Several common comorbidities were similarly distributed among HIV+ and uninfected individuals included current or past smoking (Table 1, 69%), hypertension (64%), hyperlipidemia (40%), and psychiatric diagnoses (27%). HIV+ individuals experienced more HCV infection (35% HIV+, 15% uninfected). Uninfected individuals were more likely to experience chronic pain (49% uninfected, 36% HIV+), diabetes (33% uninfected, 22% HIV+), morbid obesity (BMI >35, 19% uninfected, 5% HIV+), or a psychiatric diagnosis (29% uninfected, 20% HIV+). HIV+ individuals demonstrated greater severity of illness than uninfected. HIV+ individuals had higher VACS Index scores (Table 1, 24 vs. 18). During the observation period HIV+ were also more likely than

Table 1. Characteristics of sample overall and by HIV status.

	Overall		HIV±		Uninfected	
	N	% by column	*N*	% by column	*N*	% by column
Totals	49285	100.0%	9473	100.0%	39812	100.0%
Age						
<50 years	10457	21.2%	2299	24.3%	8158	20.5%
50–64 years	31756	64.4%	5863	61.9%	25893	65.0%
≥65 years	7072	14.3%	1311	13.8%	5761	14.5%
Sex						
Female	1249	2.5%	199	2.1%	1050	2.6%
Male	48036	97.5%	9274	97.9%	38762	97.4%
Race						
White, nonhispanic	20302	41.2%	4154	43.9%	16148	40.6%
Black, nonhispanic	22845	46.4%	4154	43.9%	18691	46.9%
Hispanic	4320	8.8%	804	8.5%	3516	8.8%
Other/missing	1818	3.7%	361	3.8%	1457	3.7%
Medical diagnoses						
Hypertension, controlled, with Rx	21501	43.6%	3613	38.1%	17888	44.9%
Hypertension, uncontrolled	10612	21.5%	1644	17.4%	8968	22.5%
Diabetes	16000	32.5%	2059	21.7%	13941	35.0%
Hyperlipidemia	20619	41.8%	3702	39.1%	16917	42.5%
Coronary artery disease	4858	9.9%	695	7.3%	4163	10.5%
Chronic obstructive Pulmonary disease	3422	6.9%	522	5.5%	2900	7.3%
Cirrhosis	575	1.2%	169	1.8%	406	1.0%
Chronic pain	23809	48.3%	3437	36.3%	20372	51.2%
Gastroesophageal reflux disease	5348	10.9%	647	6.8%	4701	11.8%
Obesity (BMI ≥35)	8215	16.7%	449	4.7%	7766	19.5%
Psychiatric diagnoses						
Major depression	3744	7.6%	789	8.3%	2955	7.4%
Bipolar disorder	2940	6.0%	498	5.3%	2442	6.1%
Posttraumatic stress disorder	6800	13.8%	753	7.9%	6047	15.2%
Schizophrenia	2761	5.6%	218	2.3%	2543	6.4%
Any psychiatric disorder	13541	27.5%	1907	20.1%	11634	29.2%
Substance use						
Alcohol related diagnosis	5297	10.7%	820	8.7%	4477	11.2%
Drug abuse and dependence	4889	9.9%	1101	11.6%	3788	9.5%
Alcohol and/or drugs diagnoses	7437	15.1%	1402	14.8%	6035	15.2%
Current smoker	24666	50.0%	4987	52.6%	19679	49.4%
Former smoker	9112	18.5%	1575	16.6%	7537	18.9%
VACS Index score and components, median (IQR)						
Total score	NA	18 (12,28)	NA	24 (12,38)	NA	18 (12,28)
Age	NA	56 (51,62)	NA	56 (50,61)	NA	57 (51,62)
HIV-1 RNA	NA	NA	NA	<400 copies	NA	NA
$CD4^+$ cell count	NA	NA	NA	515 (347,720)	NA	NA
Hemoglobin	NA	14 (13,15)	NA	14 (13,15)	NA	14 (13,15)
FIB4	NA	1.23 (0.91,1.71)	NA	1.44 (1.04,2.08)	NA	1.19 (0.89,1.63)
Estimated glomerular filtration rate	NA	87 (73,101)	NA	86 (72,102)	NA	87 (73,101)
Hepatitis C infection (col%)	9393	19.1%	3257	34.4%	6136	15.4%
Medication classes						
ACE inhibitors	16330	33.1%	2467	26.0%	13863	34.8%
Beta blockers	13972	28.3%	2064	21.8%	11908	29.9%
Diuretics	10203	20.7%	1442	15.2%	8761	22.0%
Calcium channel blockers	11492	23.3%	1348	14.2%	10144	25.5%
Lipid-lowering agents	24927	50.6%	3979	42.0%	20948	52.6%
Oral glucose-lowering agents	9727	19.7%	1016	10.7%	8711	21.9%
Gastric medications	14814	30.1%	1823	19.2%	12991	32.6%
Antidepressants	15322	31.1%	3021	31.9%	12301	30.9%
Nonopioid analgesics	12744	25.9%	1779	18.8%	10965	27.5%
Genitourinary agents	9806	19.9%	1840	19.4%	7966	20.0%
Outcomes						
Hospitalizaton	27400	55.6%	5505	58.1%	21895	55.0%
Death	7169	14.5%	1594	16.8%	5575	14.0%

uninfected individuals to be hospitalized (58 and 55%) or die (17 and 14%).

Common non-antiretroviral medications were similar in both groups. Among HIV+ and uninfected individuals, respectively, the 10 most commonly received medication classes were lipid-lowering medications (Table 1, 42 and 53%), ACE-inhibitors (26 and 35%), antidepressants (32 and 31%), gastric medications (19 and 33%), beta-blockers (22 and 30%), nonopioid analgesics (19 and

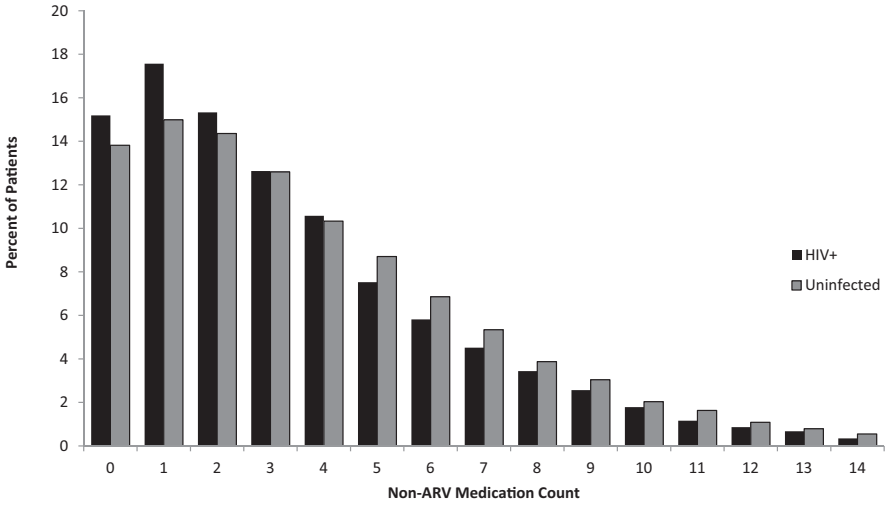

Fig. 1. Nonantiretroviral medication count by HIV status.

28%), calcium channel blockers (14 and 26%), diuretics (15 and 22%), genitourinary agents (19 and 20%), and hypoglycemic medications (11 and 22%). Of note, long-term prescription opioids (17 and 21%) were commonly prescribed to both HIV+ and uninfected individuals and proton pump inhibitors, by far the most common gastric medications, were also commonly used for more than 90 days (19 and 32%), respectively. The distribution of non-antiretroviral medication count was fairly similar among HIV+ and uninfected with HIV+ having slightly lower counts (Fig. 1). Median (5th and 95th) non-antiretroviral medication count was 3 (1, 10) among HIV+, and 4 (1, 11) among uninfected.

Characteristics associated with nonantiretroviral polypharmacy

In bivariate analyses, characteristics of HIV+ and uninfected individuals associated with non-antiretroviral polypharmacy, whether defined as more than two or at least five non-antiretrovirals, were similar (Table 2). Older age was strongly associated with polypharmacy. Those 50–64 were twice as likely, and those 65 and over, nearly three times as likely, to experience non-antiretroviral polypharmacy compared with those less than 50 years of age. Although HIV+ men were as likely as HIV+ women to experience non-antiretroviral polypharmacy, uninfected men were 20–40% more likely than uninfected women to experience polypharmacy. Whites were about 20% more likely than other racial groups to experience non-antiretroviral polypharmacy. Conditions that more than doubled the odds of non-antiretroviral polypharmacy in both groups included: hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, and psychiatric diagnoses. Some common minor conditions doubled the probability of non-antiretroviral polypharmacy including: hyperlipidemia and gastro-esophageal reflux. Interestingly, HCV infection, alcohol, and drug use disorders were more associated with polypharmacy among HIV+ than uninfected (~30–60% increased risk for HIV+ versus 10% for uninfected).

VACS Index scores were similarly and moderately correlated with non-antiretroviral medication count among HIV+ and uninfected (Spearman correlation HIV+: 0.21 95% CI 0.19, 0.23; uninfected: 0.21 95% CI 0.20, 0.22). VACS Index discriminated risk of hospitalization (HIV+ C- statistic: 0.62 95%CI 0.61, 0.63; uninfected C-statistic: 0.60, 95% CI 0.60, 0.60) and mortality (HIV+ C-statistic: 0.72, 95% CI 0.71, 0.74; uninfected C-statistic: 0.70, 95% CI 0.70, 0.71) nearly as well among uninfected as HIV+.

Nonantiretroviral polypharmacy and hospitalization

In unadjusted analyses, more than two and at least five non-antiretroviral polypharmacy was associated with increased risk of hospitalization (Table 3, >2: hazard ratio 1.68; 95% CI 1.63–1.73; ≥5: hazard ratio 1.69; 95% CI 1.65–1.73). Adjusting for demographic factors and severity of illness, more than two and at least five non-antiretroviral polypharmacy remained independently associated with hospitalization (>2: hazard ratio 1.51; 95% CI 1.47–1.55: ≥5: hazard ratio 1.52, 95% CI 1.49–1.56). Risk of hospitalization associated with polypharmacy was similar by HIV status in analyses adjusted for demographics and severity of illness (P for interaction = 0.85).

In unadjusted and adjusted analyses, compared with those on two or fewer non-antiretroviral medications, non-antiretroviral polypharmacy demonstrated a dose–response association with risk of hospitalization among HIV+ and uninfected (Fig. 2). Whenever non-antiretroviral medication count was modeled as a continuous variable (Table 4), we observed an 8% incremental increased risk of hospitalization with each

Table 2. Association of characteristics with nonantiretroviral polypharmacy (more than two and at least five medications).

	Polypharmacy prevalence (%)				Odds ratio for polypharmacy			
	More than two Non-ARVs		At least five non-ARVs		More than two non-ARVs		At least five non-ARVs	
Characteristic	HIV+	Uninfected	HIV+	Uninfected	HIV+	Uninfected	HIV+	Uninfected
All	67.2	71.2	34.1	39.3	na	na	na	na
Age								
<50 years	53.1	58.2	22.3	27.1	Ref	Ref	Ref	Ref
50–64 years	70.6	73.6	36.7	41.8	2.1	2.0	2.0	1.9
65+ years	77.0	78.9	43.3	45.2	3.0	2.7	2.7	2.2
Sex								
Female	67.3	64.2	35.7	35.5	Ref	Ref	Ref	Ref
Male	67.2	71.4	34.1	39.4	1.0	1.4	0.9	1.2
Race								
White	69.5	74.1	37.6	42.1	Ref	Ref	Ref	Ref
Black	65.4	69.9	31.4	38.3	0.8	0.8	0.8	0.9
Hispanic	68.5	69.8	35.1	37.8	1.0	0.8	0.9	0.8
Hypertension								
None	51.9	50.1	19.9	19.2	Ref	Ref	Ref	Ref
Controlled, with Rx	83.4	85.6	50.3	54.2	4.6	5.9	4.1	5.0
Uncontrolled	71.2	72.9	35.2	38.6	2.3	2.7	2.2	2.7
Diabetes								
No	63.2	65.4	29.2	32.0	Ref	Ref	Ref	Ref
Yes	81.8	81.9	51.7	52.8	2.6	2.4	2.6	2.4
Hyperlipidemia								
No	62.7	65.5	29.4	33.4	Ref	Ref	Ref	Ref
Yes	74.3	78.9	41.5	47.3	1.7	2.0	1.7	1.8
CAD/MI								
No	65.6	69.1	32.2	36.6	Ref	Ref	Ref	Ref
Yes	88.2	89.3	59.1	61.9	3.9	3.7	3.1	2.8
COPD								
No	66.4	70.0	32.9	37.6	Ref	Ref	Ref	Ref
Yes	82.2	86.1	55.6	60.0	2.3	2.7	2.6	2.5
Cirrhosis								
No	67.0	71.1	33.9	39.2	Ref	Ref	Ref	Ref
Yes	79.9	80.5	46.2	42.4	2.0	1.7	1.7	1.1
Pain-related diagnoses								
None	60.6	65.6	26.4	31.6	Ref	Ref	Ref	Ref
Acute	69.3	70.1	35.1	38.5	1.5	1.2	1.5	1.4
Chronic	77.5	76.1	46.3	46.0	2.2	1.7	2.4	1.8
Gastroesophageal reflux disease								
No	66.3	69.8	32.7	37.6	Ref	Ref	Ref	Ref
Yes	80.5	81.6	53.6	51.6	2.1	1.9	2.4	1.8
Morbid obesity (BMI ≥35)								
No	66.8	69.3	33.6	36.7	Ref	Ref	Ref	Ref
Yes	75.7	79.0	44.8	50.0	1.5	1.7	1.6	1.7
Major depression								
No	66.0	70.3	32.6	38.1	Ref	Ref	Ref	Ref
Yes	80.6	82.9	50.8	54.1	2.1	2.1	2.1	1.9
Bipolar disorder								
No	66.5	70.6	33.2	38.5	Ref	Ref	Ref	Ref
Yes	79.9	80.4	50.4	50.4	2.0	1.7	2.0	1.6
PTSD								
No	65.7	69.0	32.1	36.3	Ref	Ref	Ref	Ref
Yes	85.4	83.4	57.8	56.1	3.1	2.2	2.9	2.2
Schizophrenia								
No	66.8	70.4	33.6	38.2	Ref	Ref	Ref	Ref
Yes	85.3	82.8	56.4	55.2	2.9	2.0	2.6	2.0
Any psychiatric disorder								
No	63.5	66.7	29.5	33.3	Ref	Ref	Ref	Ref
Yes	82.0	82.2	52.6	53.8	2.6	2.3	2.7	2.3
Alcohol-related diagnosis								
No	66.4	70.9	33.4	39.0	Ref	Ref	Ref	Ref
Yes	76.1	73.2	42.0	41.2	1.6	1.1	1.4	1.1
Drug abuse and dependence								
No	66.3	71.0	33.3	39.1	Ref	Ref	Ref	Ref
Yes	74.3	73.1	40.2	41.0	1.5	1.1	1.3	1.1
Smoking								
Never	64.6	68.7	31.3	36.1	Ref	Ref	Ref	Ref
Current	67.0	71.6	33.9	39.9	1.1	1.2	1.1	1.2

Table 2 (*continued*)

	Polypharmacy prevalence (%)				Odds ratio for polypharmacy			
	More than two Non-ARVs		At least five non-ARVs		More than two non-ARVs		At least five non-ARVs	
Characteristic	HIV+	Uninfected	HIV+	Uninfected	HIV+	Uninfected	HIV+	Uninfected
Former	72.3	74.5	39.4	43.0	1.4	1.3	1.4	1.3
Hepatitis C infection								
No	64.7	70.8	32.3	39.0	Ref	Ref	Ref	Ref
Yes	72.1	73.2	37.7	40.8	1.4	1.1	1.3	1.1
Hospitalizaton								
No	57.7	63.3	23.9	29.6	Ref	Ref	Ref	Ref
Yes	74.1	77.7	41.5	47.2	2.1	2.0	2.3	2.1
Death								
No	65.3	69.4	31.6	37.0	Ref	Ref	Ref	Ref
Yes	76.8	82.5	46.7	53.5	1.8	2.1	1.9	2.0

All bivariate odds ratios significant at $P < 0.001$ except as noted. HIV+, sex $P = 0.98$, uninfected, drug abuse and dependence $P = 0.006$. ARV, antiretroviral therapy.

additional non-antiretroviral medication for HIV+ and uninfected (hazard ratio 1.08, 95% CI 1.08–1.08, P for interaction = 0.99).

Nonantiretroviral polypharmacy and mortality

In unadjusted analyses, more than two non-antiretroviral polypharmacy was associated with 68% increased risk of mortality among HIV+ (Table 3, >2: hazard ratio 1.68, 95% CI 1.50–1.89) and a 99% increased risk among uninfected individuals (hazard ratio 1.99, 95% CI 1.86–2.14, P for interaction = 0.01). Using the at least five threshold in unadjusted analysis, polypharmacy was associated with an 83% increased risk of mortality in both HIV+ and uninfected (P for interaction = 0.1, ≥5: hazard ratio : 1.83, 95% CI 1.75–1.82).

In fully adjusted models, more than two non-antiretroviral polypharmacy was associated with a 20% increased risk of mortality among HIV+ (>2: hazard ratio 1.20, 95% CI 1.07–1.36) and a 49% increased risk among uninfected (>2: hazard ratio 1.49, 95% CI 1.39–1.60, P for interaction = 0.002). The fully adjusted model of at least five non-antiretroviral polypharmacy demonstrated a 43% increased risk of mortality among HIV+ and uninfected (≥5: hazard ratio 1.43, 95% CI 1.36–1.50, P for interaction = 0.1).

In unadjusted and adjusted analyses, compared with those on two or fewer non-antiretroviral medications, we observed a dose–response association between non-antiretroviral polypharmacy and risk of mortality among HIV+ and uninfected (Fig. 2). Whenever non-antiretroviral medication count was modeled as a continuous variable (Table 4), we observed a 5% increase in risk of mortality with each additional non-antiretroviral medication among HIV+ (hazard ratio 1.05, 95% CI 1.03–1.06), and a 7% increase among uninfected (hazard ratio 1.07, 95% CI 1.06–1.07).

Discussion

In this large cohort of HIV+ and demographically similar uninfected individuals, non-antiretroviral polypharmacy

Table 3. Unadjusted and adjusted hazard ratios for nonantiretroviral therapies polypharmacy (more than two and at least five medications), hospitalization, and mortality by HIV status.

	Polypharmacy (more than two non-ARVs)						Polypharmacy (at least five non-ARVs)					
	Unadjusted			Fully Adjusted			Unadjusted			Fully Adjusted		
	Hazard ratio	95% CI		Hazard ratio	95% CI		Hazard ratio	95% CI		Hazard ratio	95% CI	
Combined	1.68	1.63	1.73	1.51	1.47	1.55	1.69	1.65	1.73	1.52	1.49	1.56
HIV+	1.72	1.62	1.83	1.50	1.41	1.60	1.73	1.64	1.83	1.53	1.45	1.62
Uninfected	1.67	1.62	1.73	1.50	1.45	1.55	1.69	1.64	1.73	1.51	1.47	1.55
Combined		na[b]			na[b]		1.83	1.75	1.92	1.43	1.36	1.50
HIV+	1.68	1.50	1.89	1.20	1.07	1.36	1.79	1.62	1.97	1.32	1.20	1.46
Uninfected	1.99	1.86	2.14	1.49	1.39	1.60	1.86	1.77	1.96	1.45	1.37	1.52

Hazard ratios are expressed in terms of non-ARV polypharmacy using a more than two or a at least five medication threshold. Fully adjusted models were adjusted for VACS Index score, age, sex, and race/ethnicity. ARV, antiretroviral therapy; CI, confidence interval. [a]Interaction between polypharmacy, HIV, and hospitalization was not significant in any model.
[b]Interaction between polypharmacy, HIV, and mortality was significant in more than two non-ARV models (unadjusted model $P = 0.01$, adjusted model $P = 0.002$), but not in at least 5 models.

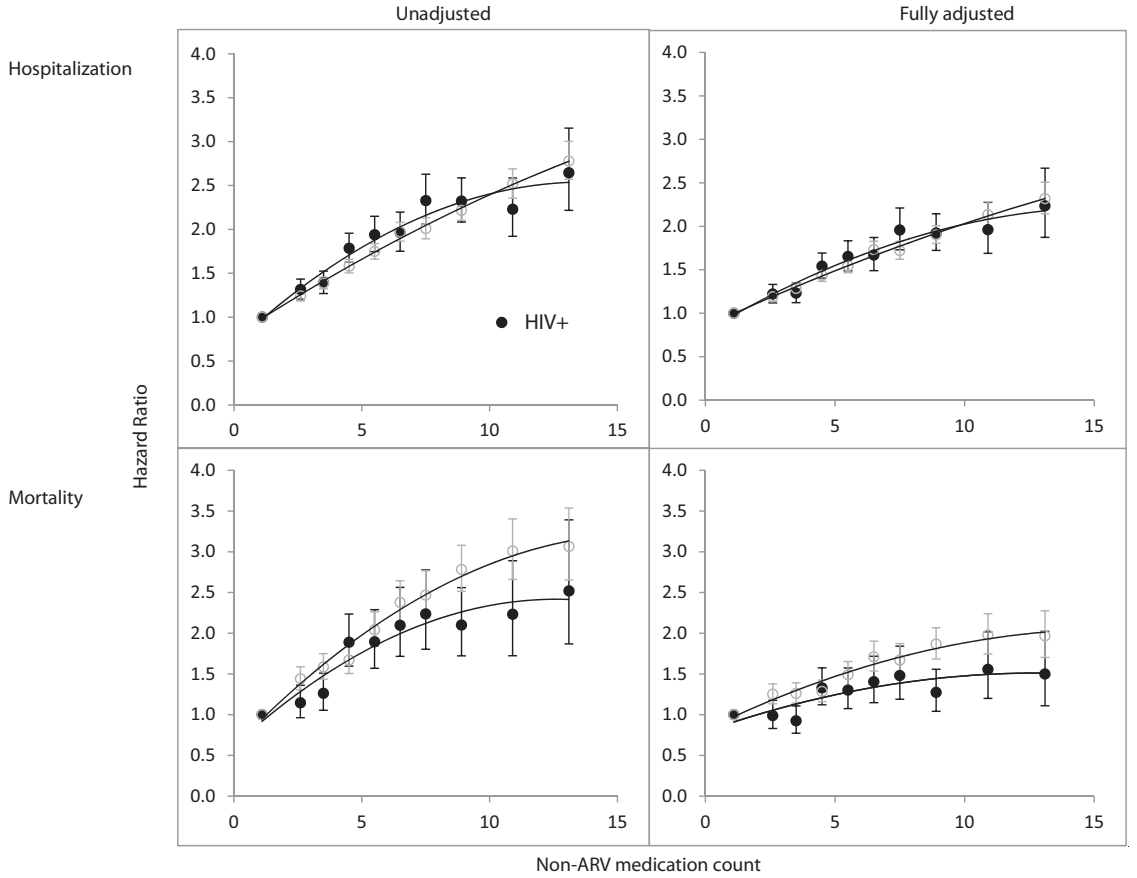

Fig. 2. Association of nonantiretroviral medication count and adverse health outcomes. Fully adjusted estimates are adjusted for VACS index, age, race/ethnicity, and sex. Models were stratified by HIV status. Solid circles represent HIV+, hollow circles represent uninfected individuals. ARV, antiretroviral.

Table 4. Unadjusted and adjusted hazard ratio of nonantiretroviral medication count (continuous measure), hospitalization and mortality by HIV status.

	Unadjusted Non-ARV medication count			Fully adjusted Non-ARV medication count		
Outcome	Hazard ratio	95% CI		Hazard ratio	95% CI	
Hospitalization[a]						
Combined	1.10	1.09	1.10	1.08	1.08	1.08
HIV+	1.10	1.09	1.10	1.08	1.07	1.09
Uninfected	1.12	1.09	1.15	1.08	1.07	1.08
Mortality[b]						
Combined		na[b]			na[b]	
HIV+	1.11	1.10	1.11	1.05	1.03	1.06
Uninfected	1.27	1.20	1.34	1.07	1.06	1.07

Hazard ratios are expressed in terms of risk associated with each additional non-ARV medication. Fully adjusted models were adjusted for VACS Index score, age, sex, and race/ethnicity. ARV, antiretroviral therapy; CI, confidence interval.

[a]*P* for interaction between polypharmacy, HIV, and hospitalization was not significant (adjusted model $P = 0.99$).

[b]*P* for interaction between polypharmacy, HIV, and mortality was significant (adjusted model $P = 0.04$).

demonstrates a dose–response association with hospitalization and mortality and neither severity of illness nor demographic factors explain these associations. Short of a randomized trial, these results provide important evidence that non-antiretroviral polypharmacy contributes to adverse health events among those aging with and without HIV infection.

Our study extends prior literature in several ways [2–5,7–10]. We had direct access to pharmacy-dispensing data in a national system with generous pharmaceutical coverage. As patients fail to fill many prescriptions, data on medication orders (prescriptions) are less informative than dispensing data. We are also the first to consider the association of non-antiretroviral polypharmacy with actual clinical outcomes among HIV+ rather than potential drug interactions or other possible adverse effects. We consider adverse associations with polypharmacy using two potential thresholds for non-antiretroviral polypharmacy (>2 and ≥5) and as a continuous measure (non-antiretroviral medication count). We are the first to compare health outcomes associated with

polypharmacy among HIV+ with demographically similar uninfected individuals. Our hospitalization data is completely parallel among HIV+ and uninfected and include events occurring within the VA system, fee for service, and care supported by other United States governmental sources (Medicare and Medicaid). Similarly, VA mortality data are very complete [23]. Finally, a major innovation of our study is our ability to adjust for severity of illness using a widely validated and accurate physiologic index.

Although many have suggested that the association between polypharmacy and adverse health outcomes is because of confounding by indication – sicker patients take more medications – our analysis suggests otherwise. The VACS Index is a widely validated, highly discriminating, physiologic index predictive of hospitalization and mortality among veterans with and without HIV infection [16–20]. The VACS Index meets or exceeds the discrimination of prior indices validated among older individuals [26]. Yet, the correlation between the VACS Index and non-antiretroviral polypharmacy was only moderate and full adjustment for the Index, age, race/ethnicity, and sex did not 'explain' the association between non-antiretroviral polypharmacy and hospitalization or mortality. After these adjustments, non-antiretroviral polypharmacy remained independently associated with hospitalization and mortality in a dose–response manner. Thus, although demographic factors, especially age, and severity of illness are associated with polypharmacy and health outcomes, neither appear to be major confounders of the association between polypharmacy and adverse health outcomes.

Instead, particular diagnoses (not all of which are associated with hospitalization or mortality), individual provider styles, and other factors not directly related to prognosis, may contribute more to polypharmacy than previously appreciated. For example, diagnoses of hyperlipidemia or gastroesophageal reflux roughly doubled the probability of non-antiretroviral polypharmacy and medication-controlled hypertension increased the probability of non-antiretroviral polypharmacy more than five times. Importantly, over 6 years of observation, none of these conditions conferred an increased risk of mortality independent of non-antiretroviral medication count, VACS Index score, and demographic factors (data not otherwise shown). Of note, these associations were similar by HIV status suggesting similar factors drive polypharmacy among those with and without HIV infection and suggesting potential targets for future intervention.

Likely mechanisms of injury from polypharmacy among HIV+ and uninfected individuals include cumulative toxicity, side effects, and drug–drug interactions [2,3]. As those with HIV age, the problem of adverse health outcomes because of non-antiretroviral polypharmacy may grow. Although antiretrovirals extend survival, they must be taken for the rest of the patient's life. antiretroviral initiation often precipitates polypharmacy a decade earlier for HIV+ than uninfected individuals [6]. Antiretrovirals interact with a wide range of common medications including lipid-lowering agents, antihypertensives, antidepressants, proton-pump inhibitors, and prescription opioids [27]. Additionally, compared with uninfected individuals, HIV+ had higher VACS Index scores indicating increased physiologic frailty and susceptibility to drug injury.

For example, 18% of HIV+ in our sample were on a proton-pump inhibitor for more than 90 days. Most protease inhibitors and several nonnucleoside reverse transcriptase inhibitors interact with proton-pump inhibitors [5]. In most circumstances, proton-pump inhibitors should not be prescribed for more than 30 days. Further, proton-pump inhibitors are associated with a growing list of serious adverse effects to which HIV+ may have increased susceptibility including fragility fractures, cognitive difficulties, and malabsorption [28].

Some might argue that comorbid conditions among HIV+ on antiretrovirals are undertreated. As observed in this study, non-antiretroviral medications are less commonly dispensed to HIV+ than to uninfected individuals. For example, HIV+ were less likely to receive lipid-lowering therapy for indicated cardiovascular disease prevention [29]. Whether this reflects a primary focus on antiretrovirals, a judicious under use related to concerns about polypharmacy; lack of comfort with non-HIV care, or clinical oversight remains to be determined. Hundreds of trials have been conducted considering whether adding a specific medication or set of medications improves outcomes, few interventions to reduce polypharmacy (deprescribe) have been tested. Most deprescribing trials failed to reduce medications because they are typically required to comply with disease-specific guidelines developed without consideration of multimorbidity or polypharmacy [30]. For every medication to treat a symptom that the trialists stopped, medications for primary and secondary prevention of disease were added. Only a randomized trial can determine whether deprescribing reduces hospitalization or mortality among those exposed to polypharmacy. Our analyses offer stronger evidence than previously reported, either among HIV infected or the general population, that polypharmacy may cause excess hospitalization and mortality. This evidence may help inform the equipoise necessary for randomized trials of deprescribing among patients with non-antiretroviral polypharmacy.

Substantial work is needed to determine how best to proceed. Although many studies in uninfected populations cite five medications as a critical threshold, no study has established the definitive threshold for non-antiretroviral polypharmacy. An important strength of our analyses is that we considered two thresholds for non-antiretroviral

polypharmacy (>2 and ≥5) as well as analyzing non-antiretroviral medication count as a continuous variable. Our analyses suggest that harms accrue in a monotonically increasing manner with three or more non-antiretroviral medications for HIV+ and uninfected individuals.

Thresholds for injury from polypharmacy likely depend on the specific regimen, the individual's underlying physiologic injury, and genetic susceptibility. Sophisticated computer models will likely be needed, incorporating knowledge such as that contained in databases of the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to account for what is known about drug–drug and drug and common substance use interactions. Current criteria such as Beers or START/STOPP were developed among uninfected individuals over 65 years of age, and evidence for the effectiveness of these criteria in avoiding actual adverse health outcomes is contradictory and limited. HIV+ on lifelong antiretrovirals, may continue to use alcohol and other substances that may also interact with their medications, and may require special consideration.

Beyond nonrandom assignment, our findings should be interpreted in light of the following limitations. We did not consider specific antiretroviral classes or agents, the number of antiretrovirals in use, or the association of specific non-antiretroviral medication classes or individual non-antiretroviral medications with hospitalization or mortality. We did not consider 'potentially inappropriate' medications in light specific antiretrovirals, advanced age, other non-antiretroviral medications or classes, or the use of alcohol. We did not study the effect of adding or subtracting a medication. Such analyses are needed, but are beyond the scope of this study. Our non-antiretroviral medication count was based on medications dispensed within the US Veterans Affairs Healthcare System (VA) and do not reflect outside prescriptions, over the counter, or complimentary medications making our measures of non-antiretroviral medication count and polypharmacy conservative. Although HIV+ in our sample were demographically similar to uninfected, the strict 1 : 2 matching employed in the VACS cohort was not preserved after the exclusions required for this analysis were applied. Finally, our analysis should be replicated in other healthcare systems.

Conclusion

Accounting for demographics and severity of illness, both HIV+ and uninfected individuals experience increasing risk of hospitalization and mortality when exposed to increasing counts of non-antiretroviral medication. Future research is needed to determine the impact of eliminating medications not essential for quality of life and survival among those aging with HIV infection.

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Conflicts of interest

There are no conflicts of interest.

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