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Polypharmacy, Drug-Drug Interactions, and Potentially Inappropriate Medications in Older HIV-Infected Adults

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Abstract

Objectives—To describe the frequency of medication-related problems in older HIV-infected adults

Design—Retrospective chart review

Setting And Participants—Community dwelling HIV-infected adults age 60 and older and age and sex-matched HIV-uninfected adults

Measurements—Total number of medications, potentially inappropriate medications as defined by the modified Beers criteria, anticholinergic drug burden as defined by the Anticholinergic Risk Scale, and drug-drug interactions using Lexi-Interact online drug interactions database.

Results—Of 89 HIV-infected participants, most were Caucasian (91%) and male (94%) with a median age of 64 (range 60-82). Common comorbidities included hyperlipidemia, hypertension, and depression. Participants were taking a median of 13 medications (range 2-38), of which only a median of 4 were antiretrovirals. At least one potentially inappropriate medication was prescribed in 46 participants (52%). Sixty-two (70%) participants had at least one Category D (consider

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therapy modification) drug-drug interaction and 10 (11%) had a Category X (avoid combination) interaction. One-third of these interactions were between two non-antiretroviral medications. We identified 15 participants (17%) with an anticholinergic risk scale score ≥3. In contrast, HIV-uninfected participants were taking a median of 6 medications, 29% had at least one potentially inappropriate medication, and 4% had an anticholinergic risk scale score ≥ 3 (p-value <0.05 for each comparison except p=0.07 for anticholinergic burden).

Conclusion—HIV-infected older adults have a high frequency of medication-related problems, of which a large portion is due to medications used to treat comorbid diseases. These medication issues were substantially higher than HIV-uninfected participants. Attention to the principles of geriatric prescribing is needed as this population ages in order to minimize complications from multiple medication use.

Keywords

polypharmacy; hiv infection; drug interactions; inappropriate prescribing

INTRODUCTION

The HIV-infected population in the United States is aging; it is estimated that over half of all persons living with HIV will be older than age 50 by 2015.[1] This phenomenon is primarily the result of successful development of antiretroviral therapy that can suppress viral replication to undetectable levels, although new infections in older adults also occur. This newly aging population is increasingly being burdened by diseases seen in older HIV-uninfected adults.[1] For example, studies demonstrate that HIV-infected patients may be at increased risk for age related comorbidities such as cardiovascular disease,[2] chronic pulmonary disease,[3] osteoporosis,[4] and cognitive impairment.[5,6] A frailty related phenotype has been seen in HIV-infected adults at a younger age compared to HIV-uninfected persons, especially in more advanced HIV infection.[7,8] HIV infection may synergistically interact with age to contribute to functional decline.[9]

As a consequence of both HIV and comorbid disease burden, polypharmacy and medication-related problems are emerging as an important challenge facing older HIV-infected adults. In the general population of adults 65 and older, comorbid disease burden and polypharmacy are associated with adverse drug events, drug-drug interactions, potentially inappropriate medications, and poor adherence to medications.[10] Combination antiretroviral therapy, which consists of at least three medications, together with medications needed to treat comorbidities makes this population at high risk for polypharmacy. Advances in combination antiretroviral therapy have resulted in single combination pills, which has improved adherence to therapy, however overall pill burden has not changed due to the non-HIV medication pill burden.[11]

Prior research supports that polypharmacy and medication-related problems such as drug-drug interactions are an important issue for HIV-infected adults.[12,13] However, only a few studies have specifically focused on older HIV-infected adults (age 50 and older) and these studies have reported different frequencies of drug-drug interactions and have not always examined interactions between non-antiretroviral medications. [14-16] Little is known about

specific prescribing issues important to older adults such as potentially inappropriate medication use and anticholinergic burden of medications in this population. As the HIV-infected population may have increased risk of age related diseases and is entering the age range in which geriatric medication issues have traditionally been studied, examination of these prescribing issues can help identify the frequency of different medication-related problems and guide efforts to improve prescribing in this vulnerable population.

The aim of our study was to describe the overall medication characteristics and frequencies of polypharmacy and other medication-related problems including drug-drug interactions, potentially inappropriate medication use and anticholinergic burden of medications in a cohort of HIV-infected adults age 60 and older. These outcomes were compared to a group of age and sex matched HIV-uninfected participants.

METHODS

Participants and Data

Participants were enrollees in the University of California San Francisco HIV Over 60 Cohort, a study of community dwelling adults over age 60 living in the greater San Francisco area.[17] Participants were recruited through community fliers, word-of-mouth and referrals from community physicians. This cohort was originally designed to investigate cognitive impairment in older HIV-infected adults and exclusion criteria included non-English speakers and participants with a history of neurological conditions that could independently impact cognition, including stroke, opportunistic brain infection, learning disability, active major medical illness, loss of consciousness greater than 30 min, and current cocaine or methamphetamine use. Demographic data, HIV history, and comorbidity data were obtained from structured interviews. Participant data, as well as data on medication usage was obtained from participants who had baseline study visits from 2008-2011.

Total medications and polypharmacy

Medication usage was obtained from review of participant medication lists during structured interviews conducted at baseline study visits. To obtain medication information, participants were mailed a questionnaire in preparation for the visit asking them to list all prescribed and over-the-counter medications taken in the previous two weeks. The examining physician (VV) reviewed this list with the subject at the time of enrollment to ensure a complete medication list was obtained. For the purposes of this study, all medications including vitamins, minerals, herbal medications and other supplements were included. Medications taken on an as needed basis were included only if the patient had taken the medication in the two weeks prior on a regular basis, defined as 4 or more days a week. For combination medications (i.e. tenofovir – emtricitabine), individual components were counted and analyzed separately. Ritonavir, when used as a boosting agent for other protease inhibitors was also counted as a separate medication. Since many participants did not report medication doses, we did not examine dosing information or pill burden. Medications were classified based on the Veterans Affairs (VA) drug classification system with the following differences: alpha blocker agents were classified as genitourinary drugs instead of

cardiovascular drugs, antihistamines were combined into the otolaryngology (ENT) category and aspirin was only included in the blood (anti-platelet) category of medications. Presence of polypharmacy was defined as being on five or more medications based on the definition commonly used in other studies[18] and we also examined presence of polypharmacy defined as being on nine or more medications, a cut-off used by federal regulatory agencies which requires further medication review for nursing home residents.[19]

Drug-drug interactions

Each participant's medication list was entered into Lexi-Interact drug interaction software (Lexi-Comp, Inc.) to generate a list of drug-drug interactions based on both pharmacokinetics and pharmacodynamics. Lexi-interact software categorizes interactions as Class A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification), and X (avoid combination).[20] We analyzed interactions categorized as D or X and further stratified these interactions as being between two antiretroviral medications, an antiretroviral medication and another class of medications, or two non-antiretroviral medications. All Lexi-Interact generated interactions were included except for those between ritonavir and other protease inhibitors since this was considered a purposeful drug interaction. For calcium, magnesium, potassium and zinc supplements a specific formulation had to be entered to generate a list of interactions. In the cases where the exact formulation was not documented on the participant's medication list, the most commonly used formulation among participants was analyzed, i.e. calcium carbonate for calcium.

As calcium carbonate formulation could influence the potential for drug-drug interactions, including interactions with specific antiretroviral agents, a sensitivity analysis was performed for the participant's medication lists where calcium formulation was not documented. This was done by analyzing the number of interactions using calcium carbonate and comparing the list to the number of interactions using calcium citrate which was the second most common formulation among participants.

All drug-drug interactions classified as D or X by Lexi-Interact were further examined by an Infectious Diseases trained clinical pharmacist (IM) to determine if the interaction was clinically significant based on cross-reference with Micromedex,[21] the American Hospital Formulary Service Drug Information,[22] and the Department of Health and Human Services (DHHS) guidelines drug interaction tables[23] and supplemented by clinical expertise.

Potentially inappropriate medications

Potentially inappropriate medication use was measured using the American Geriatrics Society updated 2012 Beers Criteria. The Beers criteria includes lists of medications and medication classes that should be avoided and drug-disease interactions that should be avoided in adults age 65 and older as determined by an expert panel.[24] As we did not have information on all of the comorbidities needed to examine drug-disease or drug-syndrome interactions, and did not have dosing information, we only analyzed medications on the Beers Criteria list independent of specific diagnosis and dose. Two medication classes on this list, non-steroidal anti-inflammatory drugs and nonbenzodiazepine hypnotics are only considered inappropriate if used chronically. As we only had data from a two week period of

time, we performed a sensitivity analysis including and excluding medications from these two medication classes. Additionally, androgens, which are commonly prescribed in HIV-infected adults,[25] are only considered inappropriate unless used for moderate to severe hypogonadism, and we performed a sensitivity analysis including and excluding androgens. Data were analyzed according to the dichotomous outcome of having at least one Beers criteria medication.

Anticholinergic burden—Anticholinergic properties of medications have been associated with delirium, cognitive impairment, dry mouth and constipation; the term anticholinergic burden refers to the cumulative effect of multiple anticholinergic medications.[26] We measured anticholinergic burden using the validated Anticholinergic Risk Scale Score.[27] The Anticholinergic Risk Scale assigns points ranging from 0-3 with 3 meaning “high anticholinergic potential” for frequently prescribed medications. To generate each participant's score, points assigned to specific medications are totaled based on the participant's medication list. A total score of ≥3 is considered clinically significant and has been shown to predict adverse events such as falls and delirium in older adults.[27] Data were analyzed as a dichotomous outcome of presence of a score ≥3.

Comparison to HIV-uninfected participants

Each of the primary measurements was examined in a group of age and gender matched HIV-uninfected participants selected from a healthy aging cohort at the same study site (University of California San Francisco Memory and Aging Center Alzheimer's Disease Research Center). Individuals in this cohort had responded to advertisements recruiting individuals without cognitive symptoms and each had completed an assessment to confirm normal cognition. All analyses were conducted using STATA v12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Simple proportions and summary statistics were used for the descriptive analyses. This study was approved by the University of California San Francisco Committee on Human Research.

RESULTS

Participant and medication characteristics

We reviewed charts from all HIV-infected participants enrolled (n= 89). Participant characteristics are summarized in **Table 1**. Most were Caucasian (91%) and male (94%) with a median age of 63 years (range 60-82) and were highly educated. The majority reported HIV risk as having sex with another man (MSM) and the median estimated duration of HIV infection (since known diagnosis of HIV) was 20 years (range 1-28). Participants had well-controlled HIV infection with a median reported CD4 T-lymphocyte cell count of 513 (interquartile range or IQR 350-700) cells/mm^3 and 84% of participants reported an undetectable viral load. Hyperlipidemia (61%), hypertension (43%) and depression (37%) were the most frequently reported comorbidities.

A total of 1,198 medications were reported with a median (interquartile range or IQR) number of medications of 13 (9-17) per participant. Of these 13 medications, 4 (IQR 3-5) were antiretroviral medications and 8 (IQR 4-14) were non-antiretroviral medications. Of

the nonantiretroviral medications, two-thirds comprised prescription medications, most commonly nervous system (27%), cardiovascular (23%), and gastrointestinal medications (11%); while the remaining one-third were vitamins or supplements. **Table 2** describes further characteristics of analyzed medications with common examples and **Figure 1** shows further breakdown of classes of non-antiretroviral medications.

HIV-uninfected participants (n=28) were similar to the HIV-infected group, being primarily Caucasian (96%) and male (86%) with a median age of 65 and were also highly educated with all participants having completed some college. Rates of hypertension (39%) and hyperlipidemia (39%) were similar to HIV-infected participants although control participants had statistically significant lower rates of depression (37% vs. 18%). Compared to HIV-infected participants, the HIV-uninfected group were taking a median of 6 (IQR 3-10) medications (p=0.03) with a median of 1 vitamin/herbal medication per participant.

Polypharmacy and Drug-Drug Interactions

Taking into account all medications, 85 (96%) participants were taking five or more medications and 68 (76%) were taking nine or more medications. Even when taking into account only nonantiretroviral medications, 66 (74%) participants still met the criteria for polypharmacy by taking five or more medications and 43 (48%) were taking nine or more medications.

Sixty-two participants (70%) had at least one Category D (consider therapy modification) drug-drug interaction with a median of 1 (range 0-15; IQR 0-3) interaction per participant. Ten participants (11%) also had a Category X interaction (avoid combination). A total of 283 interactions (171 different drug-drug interaction pairs) were identified with 267 (94%) classified as Category D and 16 (6%) classified as Category X. Most interactions were between an antiretroviral medication and a non-antiretroviral medication (152 (54%)), although approximately one-third of the interactions (99 (35%)) occurred between two non-antiretroviral agents. Fewer interactions (32 (11%)) occurred between two antiretroviral medications. Of the different drug-drug interaction pairs, 101 (60%) were deemed to be clinically significant by the clinical pharmacist. When we excluded calcium carbonate interactions in cases where the formulation of calcium was not documented, we identified 15 fewer interactions (six with antiretroviral medications and nine with non-antiretroviral medications). **Table 3** summarizes the drug-drug interactions results and lists commonly occurring examples. In the HIV-uninfected group, 8 (29%) participants had at least one drug-drug interaction ($p<0.01$), which were all classified as Category D interactions.

Potentially Inappropriate Medications and Anticholinergic Burden

At least one potentially inappropriate medication based on Beer's criteria was detected in 46 (52%) of HIV-infected participants, most frequently testosterone (n=20), ibuprofen (n=15), zolpidem (n=9), and lorazepam (n=5). As we did not have information about hypogonadism or chronicity of medications we performed sensitivity analyses. When androgens were excluded from the analysis, the number of participants with at least one potentially inappropriate medication decreased to 39 (44%); with non-steroidal anti-inflammatories and nonbenzodiazepine hypnotics excluded the number of participants decreased to 36 (40%);

and with all three classes excluded the number of participants with a potentially inappropriate medication decreased to 24 (30%).

Fifteen (17%) of participants had an Anticholinergic Risk Scale (ARS) Score of ≥ 3. The most frequent medications with anticholinergic burden were mirtazapine (n=5, 1 point on ARS), diphenhydramine (n=4, 3 points on ARS), and cetirizine (n=3, 2 points on ARS). **Figure 2** shows the percentage of HIV-infected participants with polypharmacy, drug-drug interactions, potentially inappropriate medications, and a clinically significant Anticholinergic Risk Scale Score of ≥3.

In comparison, among HIV-uninfected participants 8 (29%) had at least one potentially inappropriate medication and 1 (4%) had an Anticholinergic Risk Scale Score of ≥3 (p=0.03, 0.07 respectively compared with HIV-infected participants).

DISCUSSION

We described characteristics of medications taken by HIV-infected adults age 60 and over along with rates of polypharmacy and other medication-related problems. Participants were taking a median of 13 medications, with the majority being non-antiretroviral medications. Medications classified as treatments for neurological and cardiovascular disease were common as well as vitamin and supplement use. Medication-related problems were common among participants: 66% met criteria for polypharmacy (≥5 medications) even when antiretroviral medications were excluded, 70% had at least one drug-drug interaction, 52% had at least one potentially inappropriate medication and 17% had an Anticholinergic Risk Scale Score ≥3. Nonantiretroviral medications contributed to a majority of total medication burden and one-third of drug-drug interactions were between non-antiretroviral medications only. The frequencies of these medication-related problems were higher when compared to a group of age and sex matched HIV-uninfected participants.

Our findings provide evidence that older HIV-infected adults are at high risk for polypharmacy and medication-related problems and that the overall burden of medications in HIV-infected older adults has shifted from antiretroviral medications to medications for other comorbid diseases. Our findings also provide evidence that older HIV-infected adults may be at increased risk for prescribing issues compared to HIV-uninfected older adults. While the measures used can only identify “potential” drug-drug interactions and inappropriate medications and do not mean all of the potential drug-drug interactions or inappropriate medications will result in adverse outcomes, they do identify concerns which should be monitored. The sum of these findings stresses the importance of thinking about medication-related problems in this population and that older HIV-infected adults may benefit from medication focused strategies employed in the general elderly population.

Possible explanations for why participants had a high burden of medications include the increased burden of comorbid disease and known side effects of antiretroviral medications such as diarrhea and hyperlipidemia, which could result in additional medication use. Cardiovascular and neurological medications which were common among participants support this given increased risk of these comorbidities among HIV-infected older

adults.[2,28] We also specifically included vitamins/minerals and supplements in medication lists based on studies in both HIV-infected and uninfected adults which show a high proportion of older adults taking these types of medications;[29,30] this increases the total number of medications. Reasons medication-related problems were more common in HIV-infected patients could include that HIV providers may be less familiar with geriatric prescribing measures as well as the potential disconnect between HIV specialty care and primary care in certain settings.

While our findings provide important information about a common group of HIV-infected older adults, our findings may have less generalizability to other subgroups of HIV-infected adults. In particular, our study population consisted of highly educated, primarily Caucasian men who have sex with men (MSM), who given their viral suppression are likely highly connected to the medical system. In comparison, among persons 65 and older living with HIV infection nationally, although Caucasian men and MSM transmission comprise the largest demographic groups, rates among African-Americans and Latinos are disproportionately high .[31] The high rates of viral suppression seen are consistent with San Francisco reporting higher rates of viral suppression to the Centers for Disease Control and Prevention (CDC) and could reflect local policies to recommend early antiretroviral treatment initiation in 2010 along with widespread access to treatment.[32,33] Our study population also was infected with HIV for a median of 20 years, reflective of being diagnosed in the early days of the HIV epidemic which could also limit generalizability. However the total number of medications is similar to other studies in HIV-infected adults when vitamins and supplements were included[12] and other studies have shown cardiovascular and neurologic classes of medications are common non-antiretroviral medications.[14] High rates of vitamin/mineral and other supplement use in our study are consistent with studies of both HIV-infected adults and the general population of older adults supporting routine use of these medications.[29,30] For examining drug-drug interactions, we did not have information about dosing, which may have overestimated the number of interactions. However, the total number of drug interactions seen in this study falls within the range reported by other studies.[14,15] We only had a small number of HIV-negative controls, however when comparing with reported rates of 44% of men taking five or more medications[34] and 21% of older adults taking at least one potentially inappropriate medication[35] in the general population over age 65, the rates remain higher in the HIV-infected adults from our study.

Polypharmacy and medication-related problems will become increasingly important as the HIV-infected population ages, as reflected by the results of our study. In this population of HIV-infected adults over age 60, the burden of non-antiretroviral medications was important suggesting a shift in care from control of HIV to management of comorbid diseases. High rates of polypharmacy, drug-drug interactions, potentially inappropriate medication use and anticholinergic burden suggest that greater attention to geriatric prescribing principles and targeted HIV provider education on those principles will be useful for this population. Efforts at providing integrated, geriatric-sensitive care are needed as the HIV-infected population continues to age.

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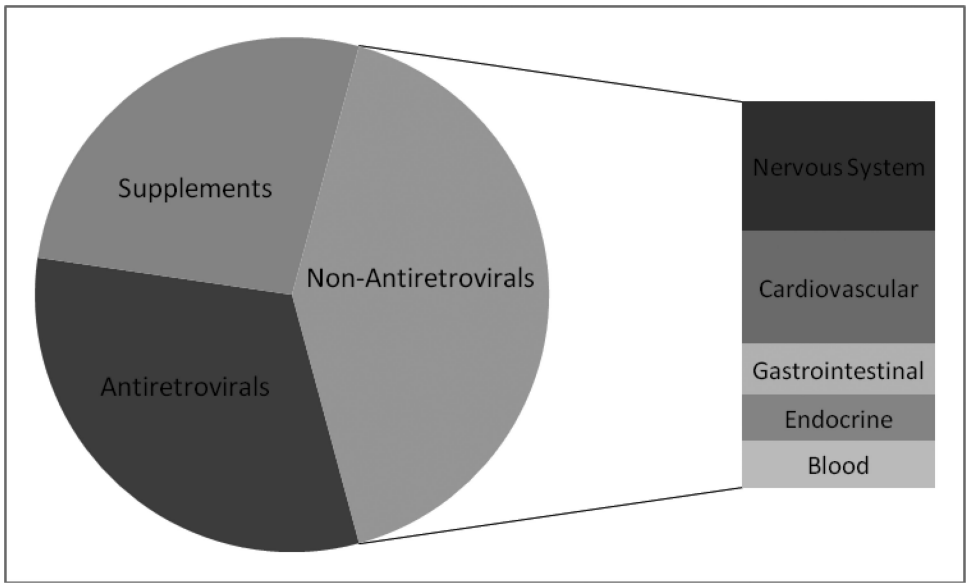

Figure 1.

Common Classes of Medications Used by HIV-Infected Participants. The pie chart shows the proportions that antiretroviral medications, nonantiretroviral medications and vitamins/minerals/supplements contributed to HIV-infected participants' total medications. The bar graph on the right shows the five most common classes of non-antiretroviral medications based on the Veterans Affairs Medication Classification System. Examples of Nervous system medications include sedative/hypnotics and antidepressants. Cardiovascular medications include antilipemic agents and beta blockers. Gastrointestinal medications include antidiarrheals and antiulcer agents (such as proton pump inhibitors). Endocrine medications include androgens and blood glucose regulation agents. Blood medications include antiplatelet and anticoagulants.

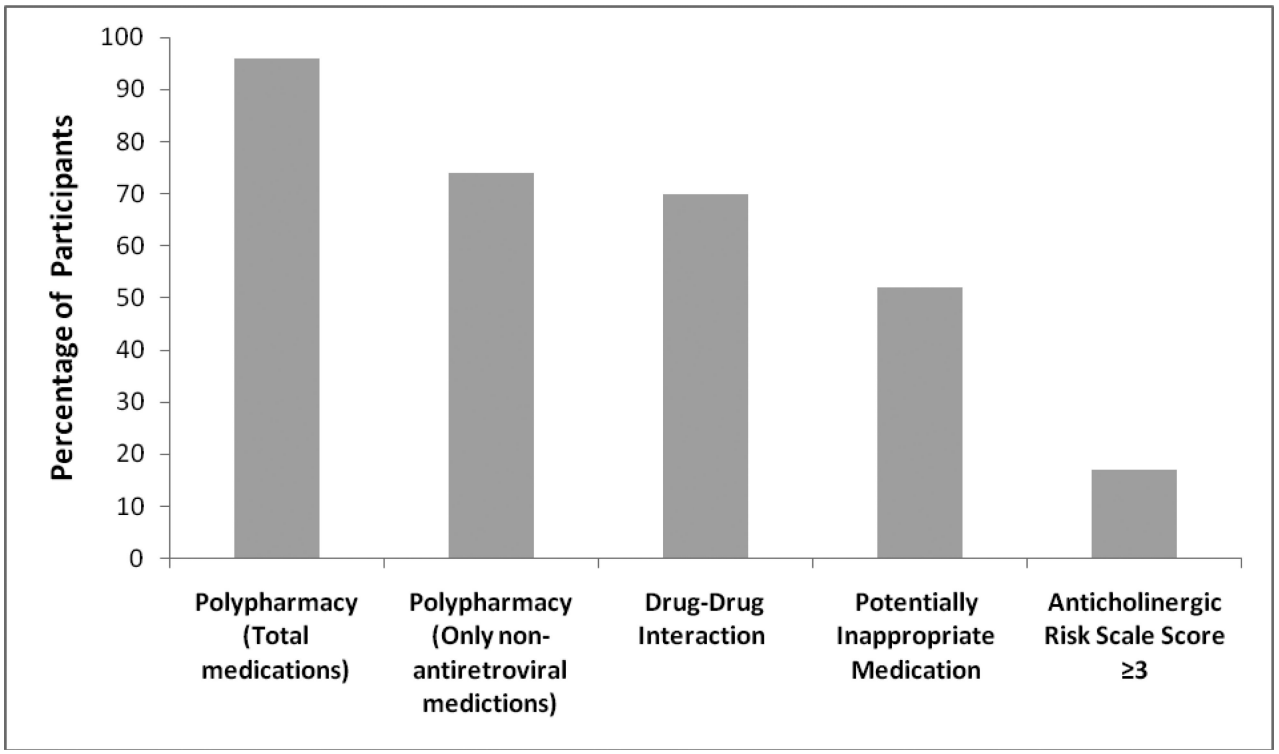

Figure 2.

Percentage of HIV-Infected Participants with Medication-Related Problems. Each bar represents the percentage of participants with each listed medication-related problem. In this figure, polypharmacy is defined as ≥5 medications.

Table 1

Participant Characteristics (n=89)

Characteristic	Median (IQR)[a] or n (%)
Age	63 (60-82)
Male	84 (94%)
Race	
Caucasian	81 (91%)
African- American	4 (5%)
HIV Risk	
MSM[b]	73 (82%)
Heterosexual	3 (3%)
IVDU[c]	2 (2%)
Mixed[d]	6 (7%)
Unknown	5 (6%)
Education	
High School or Less	7 (8%)
Some College/College Degree	47 (53%)
Advanced Degree Training	35 (39%)
HIV Characteristics	
Length of HIV Infection (years)	20 (14-24)
CD4 T-cell count (cells/mm^3)[e]	513 (350-700)
Viral suppression[f]	75 (84%)
Taking antiretroviral therapy	86 (97%)
Comorbid Conditions	
Hyperlipidemia	54 (61%)
Hypertension	38 (43%)
Depression	33 (37%)
Diabetes	10 (11%)
HAND[g]	41 (46%)

[a] IQR=interquartile range

[b] MSM= men who have sex with men

[c] IVDU=Intravenous Drug Use

[d] Mixed= More than one possible risk of HIV infection

[e] based on self-report; compared to actual lab values with median 539 (378-656) cells/mm^3

[f] based on self-report, which was confirmed by laboratory testing in 75% of participants

[g] HAND= HIV-Associated Neurocognitive Disorder: which includes Asymptomatic Neurocognitive Impairment (ANI); Mild Neurocognitive Disorder (MND); HIV Associated Dementia (HAD, n=2 (2%))

Table 2

Summary of Medications per Participant

Medication	Median (IQR)[a]	Common Examples n (%)
Total Number Medications	13 (9-17)[b]	
Antiretrovirals	4 (3-5)	tenofovir 55 (62%)
		ritonavir 43 (48%)
		emtricitabine 41 (46%)
Non-antiretrovirals	6 (3-9)	aspirin 45 (51%)
		acyclovir 22 (25%)
		atorvastatin 21 (24%)
Vitamin/Mineral/Supplements	2 (0-5)	multivitamin 48 (54%)
		omega-3 30 (34%)
		calcium 24 (27%)

[a] IQR=interquartile range

[b] Given properties of the median, the number of medications in each group does not sum to the total number of medications

Table 3

Drug-Drug Interactions Among HIV-infected Adults

	All interactions[a]	Category D[b]	Category X[c]	Common Examples[d]
Total drug-drug interactions	283	267	16	
Antiretroviral-non-antiretroviral	152 (54%)	142 (53%)	9 (56%)	Ritonavir & Atorvastatin (n=9) Atazanavir & Calcium Carbonate (n=7)
Non-antiretroviral-non-antiretroviral	99 (35%)	98 (37%)	2 (13%)	Ibuprofen & Aspirin (n=11) Atorvastatin & Niacin (n=5)
Antiretroviral-antiretroviral	32 (11%)	27 (10%)	5 (31%)	Atazanavir & Tenofovir (n=12) Ritonavir & Efavirenz (n=3)

[a] Each column reported as n (%) of total number of interactions

[b] Category D = consider therapy modification

[c] Category X = avoid combination

[d] All examples of drug-drug interactions listed were classified as Category D (consider therapy modification)