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Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive antiretroviral therapy

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Objectives: We quantified concomitant medication polypharmacy, pharmacokinetic and pharmacodynamic interactions, adverse effects and adherence in Australian adults on effective antiretroviral therapy.

Design: Cross-sectional.

Methods: Patients recruited into a nationwide cohort and assessed for prevalence and type of concomitant medication (including polypharmacy, defined as ≥5 concomitant medications), pharmacokinetic or pharmacodynamic interactions, potential concomitant medication adverse effects and concomitant medication adherence. Factors associated with concomitant medication polypharmacy and with imperfect adherence were identified using multivariable logistic regression.

Results: Of 522 participants, 392 (75%) took a concomitant medication (mostly cardiovascular, nonprescription or antidepressant). Overall, 280 participants (54%) had polypharmacy of concomitant medications and/or a drug interaction or contraindication. Polypharmacy was present in 122 (23%) and independently associated with clinical trial participation, renal impairment, major comorbidity, hospital/general practice-based HIV care (versus sexual health clinic) and benzodiazepine use. Seventeen participants (3%) took at least one concomitant medication contraindicated with their antiretroviral therapy, and 237 (45%) had at least one pharmacokinetic/pharmacodynamic interaction. Concomitant medication use was significantly associated with sleep disturbance and myalgia, and polypharmacy of concomitant medications with diarrhoea, fatigue, myalgia and peripheral neuropathy. Sixty participants (12%) reported imperfect concomitant medication adherence, independently associated with requiring financial support, foregoing necessities for financial reasons, good/very good self-reported general health and at least 1 bed day for illness in the previous 12 months.

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Conclusion: In a resource-rich setting with universal healthcare access, the majority of this sample took a concomitant medication. Over half had at least one of concomitant medication polypharmacy, pharmacokinetic or pharmacodynamic interaction. Concomitant medication use was associated with several adverse clinical outcomes.

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Introduction

Most HIV-infected patients in resource-rich settings are successfully treated with combination antiretroviral therapy (ART) [1–3]. However, up to two-thirds of these patients take a concomitant medication to mitigate ART side effects and/or to treat comorbid conditions [4–6]. Concomitant medication use is more prevalent in those with HIV than in the general population [5] and has been associated with older age, female sex, obesity and hepatitis B/C coinfection [4–7]. Concomitant medications could complicate HIV care by contributing to polypharmacy, interactions, side effects and suboptimal adherence.

Polypharmacy (commonly defined as use of five or more medications [8,9]) is associated with increased risk for morbidity, nonadherence, drug interactions and side effects in the general population [4,6,9,10], and is more common in HIV-infected adults than in the general population [4,11,12]. Polypharmacy increases with age [11,13], but is likely underestimated given that most studies in HIV-infected adults only account for prescribed medicines [4]. Polypharmacy of concomitant medications in HIV has been associated with adverse drug reactions leading to hospitalization [9] and suboptimal adherence to ART [14]; however, others have shown that initiation of concomitant medication is favourable to ART adherence [15].

Concomitant medication use in HIV-infected adults increases the risk of pharmacokinetic interactions, particularly in patients receiving a boosted protease or nonnucleoside reverse transcriptase inhibitor (due to cytochrome P450 3A inhibition) [6,16]. Furthermore, pharmacodynamic interactions between ART and concomitant medications can result in additive, antagonistic or synergistic effects of one or the other medication [17,18]. Contraindicated combinations of ART and concomitant medications have been found in 2–7% of ART-treated patients [6,19]. In one cohort, clinically significant drug–drug interactions (DDIs) were found in 27% of patients, and only 35% of these were correctly identified by clinicians [20].

Side effects of ART include nausea, diarrhoea, fatigue, sleep disturbance, myalgia, rash, lipodystrophy and peripheral neuropathy. Concomitant medications may cause similar adverse effects, and it is unknown if adverse effects are more prevalent in those who take concomitant medications or have polypharmacy.

Although there are some data on concomitant medication use and pharmacokinetic ART interactions, recent data on nonprescription medication are sparse, and potential risk factors for polypharmacy have not been evaluated against a broad range of clinical, socio-economic and behavioural parameters. Also, there are no data on adverse effects in HIV-infected patients taking concomitant medication.

Adherence to concomitant medications is important to successful HIV care and patient outcomes related to comorbidity management. Adherence to medication in general is impacted by socio-economic factors, healthcare team/system-related factors, condition-related factors, therapy-related factors and patient-related factors [21]. However, factors related to concomitant medication adherence in HIV patients treated with ART have not been evaluated. Furthermore, the relationship between ART adherence and adherence to concomitant medications is not addressed in the literature.

We previously established a national cohort of Australian adults to evaluate risks for ART failure [22]. The study recorded concomitant medication use. In the present analysis, we evaluated concomitant medication use, polypharmacy, drug interactions, adverse effects and adherence, including risks for polypharmacy and imperfect adherence.

Methods

HIV-infected adults were eligible if they were on ART, had an undetectable HIV plasma viral load, could complete study assessments (interpreter permitted) and had prerequisite standard-of-care blood results available [HIV RNA, $CD4^+$ T-lymphocyte cell count, haemoglobin, estimated glomerular filtration rate (eGFR) and alanine aminotransferase].

Participants were enrolled at 17 Australian sexual health clinics, hospital clinics and high HIV-caseload general practice sites between September 2013 and November 2015 [22]. Ethical approval was obtained from the Human Research Ethics Committee at each study site, and all participants provided written, informed consent.

We aimed to enrol a representative sample of patients from each site, not excluding patients from any demographic. Sites were instructed to invite all eligible participants sequentially (e.g. every patient at a given clinic or on a clinic day) to avoid selection bias. Enrolling patients at all sites of HIV care (sexual health clinics, hospital clinics and high HIV-caseload general practice sites) allowed for a sample that did not preference only those who may have more complex needs (e.g. those at a hospital site) or, conversely, a younger, more recently diagnosed demographic (e.g. those at a sexual health clinic). Enrolment procedures have been more extensively described previously [22]. The enrolled cohort was diverse and reflective of the HIV epidemic in Australia [23].

Study assessments are described in detail elsewhere [22]. A 204-item questionnaire completed on a dedicated laptop assessed the following themes: socio-demographics, financial and employment status, health care, treatment access, physical health, mental health, quality of life, drug and alcohol use, life stressors, social supports, HIV disclosure, HIV stigma, ART regimen (side effects, use and adherence), ART-related necessity beliefs and concerns and concomitant medication use [24–34]. Brief neurocognitive screening was completed (Cogstate [35]). Medical and HIV history, serious non-AIDS events (SNAEs) [36], comorbidities, sexually transmitted infections and laboratory data were collected.

Baseline data are presented descriptively as frequencies, percentages and sample means or medians. Multivariate analyses were conducted to determine factors associated with polypharmacy and imperfect concomitant medication adherence [including sensitivity analyses using backward-stepwise and enter (standard) methods of logistic regression, which yielded similar results (data not shown)].

Polypharmacy

Polypharmacy of concomitant medications was defined by use of at least five concomitant medications and included use of over-the-counter and alternative medications (but not ART) [8,9]. Polypharmacy was assessed using bivariate analysis with all other covariates, significant covariates ($P < 0.05$) were included in a forward-step logistic regression model.

Contraindicated medication use, pharmacokinetic or pharmacodynamic interactions

Concomitant medications were examined for DDIs with ART against each product label (Therapeutic Goods Administration Australia and USA Food and Drug Administration current approved) and cross-checked with the University of Liverpool HIV drug interactions database [37]. Combinations were classified as 'no known DDI', 'potential DDI' or 'contraindicated'. Potential DDIs were those listed as having insufficient evidence on coadministration, or evidence of pharmacokinetic or pharmacodynamic interaction, with coadministration accompanied by a caution to prescribers (e.g. increased monitoring, dosage adjustment). Contraindications were identified where there was explicit advice against coprescribing under United States, Australian or European ART guidelines. We did not examine potential DDIs between concomitant medications.

Adverse effects

Pearson's chi-squared test was used to evaluate the relationship between concomitant medication use and between polypharmacy of concomitant medications with each of the following symptoms: nausea, diarrhoea, fatigue, sleep disturbance, muscle pain/weakness, rash, peripheral neuropathy and self-reported lipodystrophy, which could be any fat redistribution.

After analysing adverse effects for associations with polypharmacy, we undertook regression analysis adjusting for comorbid disease burden. Using the previously validated Charlson comorbidity index [38], participants were assigned a score based on the presence or absence of 17 comorbid conditions, with higher scores indicating higher disease burden and mortality risk. All participants were assigned a baseline score of 6 as per the Charlson score for HIV-infection; the index score was entered into the model as a continuous variable, with the binary variable 'polypharmacy: yes or no' also in the model.

Concomitant medication adherence

Imperfect concomitant medication adherence was defined by patient-reported interruption in the previous 12 months. Covariates were assessed by bivariate analysis with concomitant medication self-reported adherence. Covariates significantly associated with adherence at bivariate analysis ($P < 0.05$) were included in a forward-step logistic regression model.

All statistical analyses were conducted in IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York, USA).

Results

Participants

Baseline characteristics of the 522 participants (significant for concomitant medication use and polypharmacy) are shown in Table 1. Four hundred and ninety-four (94.6%) were men, mean age was 50.8 years (SD 12.3), median

Table 1. Sample characteristics by concomitant medication exposure (significant covariates).

Variables	Total sample, $n=522$ *n* (%) or mean (SD)	Concomitant medications: None (0), $n=130$ *n* (%) or mean (SD)	≥1, $n=392$ *n* (%) or mean (SD)	1–4, $n=270$ *n* (%) or mean (SD)	≥5, $n=122$ *n* (%) or mean (SD)	*P* value for trend*
Demographic characteristics						
Age (years; mean, SD)	50.8 (12.3)	41.9 (12.4)	53.8 (10.8)	52 (11.0)	57.4 (9.4)	<0.001
Sex (male)	494 (94.6)	117 (90.0)	376 (96.0)	256 (94.8)	120 (98.4)	0.006
Australian born	322 (61.6)	62 (47.7)	259 (66.1)	172 (63.7)	87 (71.3)	<0.001
Living alone	212 (40.5)	28 (21.5)	183 (46.7)	117 (43.3)	66 (54.1)	<0.001
Speaks English at home	493 (94.3)	110 (84.6)	382 (97.4)	261 (96.7)	121 (99.2)	<0.001
Australian citizen	461 (88.1)	98 (75.4)	362 (92.3)	245 (90.7)	117 (95.9)	<0.001
Has Medicare access	508 (97.1)	120 (92.3)	387 (98.7)	266 (98.5)	121 (99.2)	0.001
Met Medicare safety net[a] in last 12 months	94 (18.0)	12 (9.2)	81 (20.7)	40 (14.8)	41 (33.6)	<0.001
Has private health insurance	221 (42.3)	63 (48.5)	158 (40.3)	119 (44.1)	39 (32.0)	0.010
Financial/employment status						
On social welfare	212 (40.6)	21 (16.2)	191 (48.7)	110 (40.7)	81 (66.4)	<0.001
Required financial assistance in last 12 months	138 (26.4)	23 (17.7)	127 (32.4)	78 (28.9)	49 (40.2)	<0.001
Unemployed	226 (43.2)	33 (25.4)	193 (49.2)	111 (41.1)	82 (67.2)	<0.001
Lives in public-subsidized accommodation	105 (20.1)	12 (9.2)	92 (23.5)	51 (18.9)	41 (33.6)	<0.001
In previous 12 months, for financial reasons, had to forego food, groceries, rent, household bills, furniture, clothing, white goods	114 (21.8)	17 (13.1)	97 (24.7)	62 (23.0)	35 (28.7)	0.004
HIV healthcare and treatment access						
Uses the following for HIV management						
Hospital-based HIV clinic	254 (48.7)	59 (45.4)	195 (49.7)	123 (45.6)	72 (59.0)	0.039
Community-based general practice	174 (33.3)	16 (12.3)	158 (40.3)	95 (35.2)	63 (51.6)	<0.001
Sexual health clinic/centre	168 (32.2)	56 (43.1)	112 (28.6)	79 (29.3)	33 (27.0)	0.007
Hospital pharmacy	259 (49.6)	44 (33.8)	215 (54.8)	137 (50.7)	78 (63.9)	<0.001
Drug or alcohol services	9 (1.7)	–	9 (2.3)	5 (1.9)	4 (3.3)	0.044
HIV community organization or support group	77 (14.8)	15 (11.5)	62 (15.8)	32 (11.9)	30 (24.6)	0.004
Primary HIV physician						
General practitioner	181 (34.7)	27 (20.8)	154 (39.3)	106 (39.3)	48 (39.3)	0.001
Sexual health physician	114 (21.8)	41 (31.5)	73 (18.6)	55 (20.4)	18 (14.8)	0.001
Study enrolment site						
High-caseload general practice	145 (27.8)	8 (6.2)	137 (34.9)	92 (34.1)	45 (36.9)	<0.001
Hospital-located clinic	174 (33.3)	31 (23.8)	143 (36.5)	92 (34.1)	51 (41.8)	0.002
Sexual health clinic/centre	203 (38.9)	91 (70.0)	112 (28.6)	86 (31.9)	26 (21.3)	<0.001
Duration of care from primary HIV physician (years; mean, SD)	11.3 (8.0)	7.6 (6.9)	12.4 (8.0)	11.5 (8.0)	14.6 (7.8)	<0.001
Changed primary HIV physician in last 12 months	80 (15.3)	32 (24.6)	51 (13.0)	37 (13.7)	14 (11.5)	0.016
Seen other medical specialist in last 12 months	321 (61.5)	60 (46.2)	261 (66.6)	167 (61.9)	95 (77.9)	<0.001
Other healthcare providers involved in HIV care	324 (62.1)	63 (48.5)	261 (66.6)	169 (62.6)	92 (75.4)	<0.001
Cost of non-HIV medications (A$, last 3 months; mean, SD)	145 (434)	107 (644)	157 (335)	129 (187)	224 (537)	0.041
HIV history						
HIV diagnosed prior to 1996	213 (40.8)	22 (16.9)	191 (48.7)	113 (41.9)	78 (63.9)	<0.001
Nadir $CD4^+$ T-lymphocyte cell count <200 cells/μl	202 (38.7)	34 (26.2)	168 (42.9)	112 (41.5)	56 (45.9)	<0.001
Previous AIDS	120 (22.9)	13 (10.0)	107 (27.3)	62 (23.0)	45 (36.9)	<0.001
Comorbidities						
Heart disease	57 (10.9)	2 (1.5)	55 (14.0)	24 (8.9)	31 (25.4)	<0.001
Hypertension	94 (18.0)	2 (1.5)	92 (23.5)	51 (18.9)	41 (33.6)	<0.001
Stroke	9 (1.7)	–	9 (2.3)	3 (1.1)	6 (4.9)	0.003
Peripheral vascular disease	8 (1.50)	–	8 (2.0)	3 (1.1)	5 (4.1)	0.008
Diabetes	31 (5.9)	–	31 (7.9)	13 (4.8)	18 (14.8)	<0.001
Chronic liver failure	2 (0.4)	–	2 (0.5)	–	2 (1.6)	0.038
Chronic kidney disease	14 (2.7)	–	14 (3.6)	8 (3.0)	6 (4.9)	0.015
Other diagnosed comorbidity[b]	102 (19.5)	7 (5.4)	95 (24.2)	62 (23.0)	33 (27.0)	<0.001
Current health						
Length of undetectable HIV viral load >1 year	399 (76.4)	91 (70.0)	308 (78.6)	205 (76.0)	103 (84.4)	0.007
Currently enrolled on a clinical trial	45 (8.6)	4 (3.1)	41 (10.5)	25 (9.3)	16 (13.1)	0.004
eGFR <60 ml/min per 1.73 m^2	43 (8.2)	6 (4.6)	37 (9.4)	14 (5.2)	23 (18.9)	<0.001
Hepatitis B or C coinfection	70 (13.4)	3 (2.3)	65 (16.6)	46 (17.0)	19 (15.6)	0.001

Table 1 (*continued*)

Variables	Total sample, $n=522$ *n* (%) or mean (SD)	Concomitant medications				*P* value for trend*
		None (0), $n=130$ *n* (%) or mean (SD)	≥1, $n=392$ *n* (%) or mean (SD)	1–4, $n=270$ *n* (%) or mean (SD)	≥5, $n=122$ *n* (%) or mean (SD)	
Sexually transmitted infection in last 12 months	71 (13.6)	28 (21.5)	42 (10.7)	33 (12.2)	9 (7.4)	0.001
Hospitalized for ≥1 night in last 12 months	108 (20.7)	16 (12.3)	92 (23.5)	57 (21.1)	35 (28.7)	0.001
Physical health						
Self-reported good/very good overall health	435 (83.3)	118 (90.8)	316 (80.6)	223 (82.6)	93 (76.2)	0.002
≥1 Doctor visits for illness in last 12 months	358 (68.6)	83 (63.8)	275 (70.2)	184 (68.1)	91 (74.6)	0.044
Mental health						
Major depressive disorder (PHQ-9 [24])	87 (16.7)	12 (9.2)	75 (19.1)	45 (16.7)	30 (24.6)	0.001
Psychiatric illness – currently clinically active	112 (24.3)	4 (3.1)	108 (27.6)	66 (24.4)	42 (34.4)	<0.001
Alcohol and drug use						
Benzodiazepines	39 (7.5)	–	39 (9.9)	18 (6.7)	21 (17.2)	<0.001
PDE5 inhibitor ('viagra' or 'similar')	67 (12.8)	9 (6.9)	58 (14.8)	36 (13.3)	22 (18.0)	0.008
Opiates	11 (2.1)	–	11 (2.8)	4 (1.5)	7 (5.7)	0.002
Life stressors						
>2 Major stress events in last 12 months	133 (25.5)	20 (15.4)	113 (28.8)	76 (28.1)	37 (30.3)	0.005
Social support						
Married/*de facto*/in regular relationship	226 (43.2)	64 (49.2)	158 (40.3)	147 (54.4)	87 (71.3)	0.001
In serodiscordant sexual relationship	136 (26.0)	46 (35.4)	90 (23.0)	71 (26.3)	19 (15.6)	0.047
Not linked to an HIV support organization	388 (74.3)	115 (88.5)	330 (84.2)	238 (88.1)	92 (75.4)	0.004
Antiretroviral therapy						
ART as a single-tablet regimen	158 (30.3)	55 (42.3)	103 (26.3)	81 (30.0)	22 (18.0)	<0.001
Once-daily ART dosing	333 (63.7)	102 (78.5)	231 (58.9)	169 (62.6)	62 (50.8)	<0.001
Commenced ART within 1 year of diagnosis	245 (46.8)	77 (59.2)	168 (42.9)	118 (43.7)	50 (41.0)	<0.001
Commenced ART prior to 2004	247 (47.3)	26 (20.0)	221 (56.4)	134 (50.0)	87 (71.3)	<0.001
When started ART felt 'not at all'/'only somewhat' informed about ART						
Side effects	178 (34.1)	34 (26.2)	144 (36.7)	95 (35.2)	49 (40.2)	0.020
Benefits	115 (22.0)	18 (13.8)	97 (24.7)	57 (21.1)	40 (32.8)	<0.001
Dosing requirements	44 (8.4)	7 (5.4)	37 (9.4)	22 (8.1)	15 (12.3)	0.045
Lifestyle impacts	151 (28.9)	26 (20.0)	125 (31.9)	79 (29.3)	46 (37.7)	0.002
Own ART regimen	106 (20.3)	16 (12.3)	90 (23.0)	56 (20.7)	34 (27.9)	0.003
Reason for starting ART: to prevent transmission to HIV-negative partners	101 (19.5)	36 (27.7)	65 (16.6)	45 (16.7)	20 (16.4)	0.023
Never speaks with HIV doctors or nurses about: cost burden of ART	425 (82.1)	95 (73.1)	330 (84.2)	227 (84.1)	103 (84.4)	0.025
Sometimes stops taking ART medications if feeling worse	48 (9.2)	4 (3.1)	44 (11.2)	27 (10.0)	17 (13.9)	0.005
Experienced ART side effects in last 12 months	297 (56.9)	62 (47.7)	235 (59.9)	156 (57.8)	79 (64.8)	0.007
Delayed/interrupted ART prior to 12 months ago	85 (17.5)	9 (6.9)	76 (19.4)	52 (19.3)	24 (19.7)	0.024
Concomitant medications						
Medications per day (mean, SD)	3.6 (4.3)	0 (0.0)	4.7 (4.4)	2.7 (2.0)	9.3 (4.9)	<0.001
Delayed/interrupted last 12 months	60 (14.0)	4 (3.1)	56 (14.3)	32 (11.9)	24 (19.7)	0.001
Delayed/interrupted prior to 12 months ago	49 (12.3)	3 (2.3)	46 (11.7)	26 (9.6)	20 (16.4)	0.007
PROQOL HIV						
PROQOL HIV summary score[c] (mean, SD)	40.1 (23.4)	41.8 (21.4)	41.7 (24.1)	40.8 (24.1)	49.8 (25.0)	0.005

ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; PDE5, phosphodiesterase type 5 inhibitor; PROQOL HIV, the patient reported outcomes quality of life - HIV.
[a]Whereby medical costs – including pharmaceutical copayments, are capped after reaching an annual threshold.
[b]Other diagnosed comorbidities include: depression [6 (1.1%)], erectile dysfunction [6 (1.1%)], osteoarthritis [5 (1.0%)] Chronic Obstructive Pulmonary Disease [4 (0.8%)] and asthma [4 (0.8%)].
[c]Sample summary score (mean) (higher score indicative of lower quality of life).
**P* value for trend: no comedication(s), 1–4 comedication(s), polypharmacy (≥5 comedications).

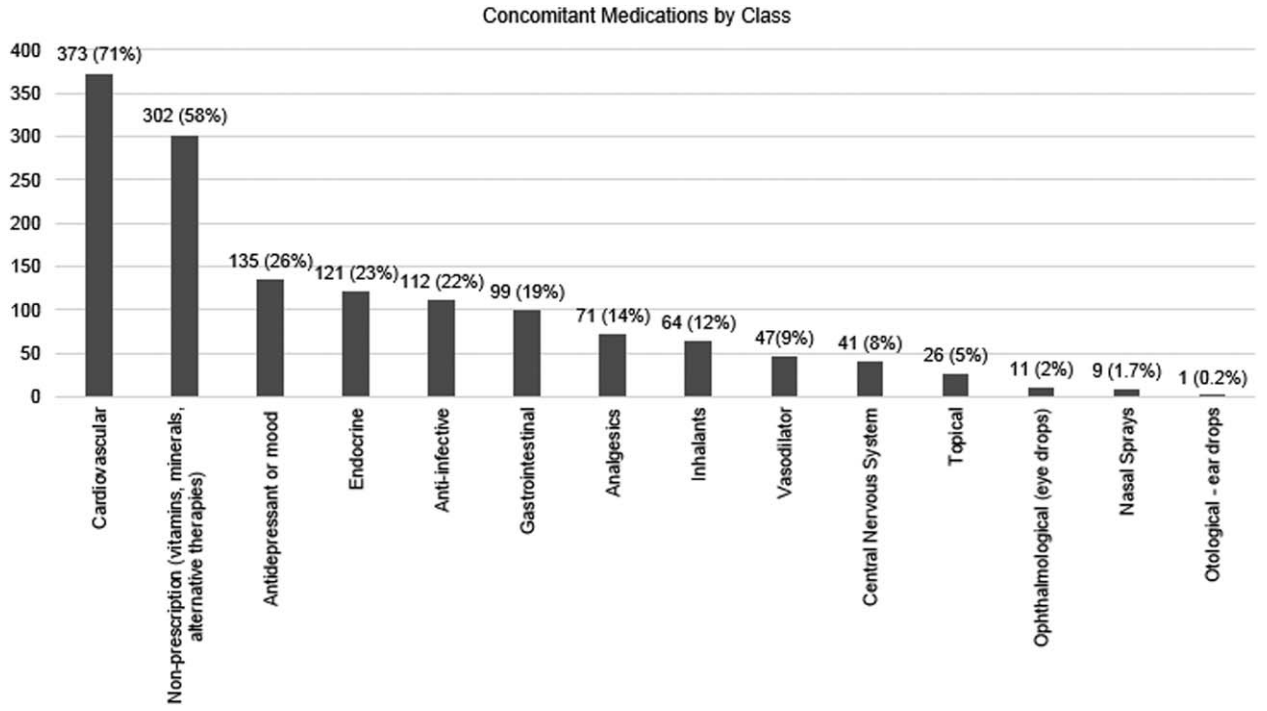

Fig. 1. Concomitant medications by system/type.

duration of HIV infection was 15.0 years [interquartile range (IQR) 7.0–25.0] and median current duration of undetectable viral load was 3.3 years (IQR 1.2–6.8). Supplementary Table 1, http://links.lww.com/QAD/B185 lists all covariates (including those that were nonsignificant).

Comorbidities were diagnosed in 292 (55.9%) participants including the following SNAEs: heart disease [57 (10.9%)], stroke [9 (1.7%)], peripheral vascular disease [8 (1.5%)], diabetes [31 (5.9%)], chronic liver failure [2 (0.4%)] and chronic kidney disease [14 (2.7%)]. Seventy (13.4%) participants had hepatitis coinfection, and 97 (18.6%) reported symptoms consistent with 'major depressive disorder' [patient health questionnaire (PHQ-9) [24]].

ART regimens are listed in Supplementary Table 2, http://links.lww.com/QAD/B185. Once-daily ART was prescribed to 333 (63.7%) participants, and 158 (30.3%) participants took a single-tablet regimen (STR), 138 (26.4%) took a boosted protease inhibitor. Alcohol, cigarette and recreational drug use are shown in Supplementary Table 3, http://links.lww.com/QAD/B185.

Concomitant medication use

Of the 522 participants, 392 (75.1%) took at least one concomitant medication, and 363 (92.6%) of those had at least one prescribed medication (versus over-the-counter, herbal/alternative medications). Among participants who took a concomitant medication, the daily concomitant pill burden was 6.0 (SD 4.5), whereas the sample ART daily pill burden was 1.2 (SD 0.4). The most common classes of concomitant medications taken were cardiovascular agents, nonprescription (vitamins, minerals and alternative therapies), antidepressants, endocrine agents and antiinfectives (Fig. 1).

Polypharmacy

Of those on a concomitant medication, 122 (31%) took at least five concomitant medications (23% of all participants). Covariates significantly associated with polypharmacy in bivariate analysis are listed in Table 2. Those independently associated with polypharmacy were enrolment in a randomized trial [adjusted odds ratio (AOR) 3.5], an eGFR less than 60 ml/min per 1.73 m^2 (AOR 3.8), a known comorbidity or SNAE (AOR 4.2), HIV management in a hospital-based clinic (AOR 2.0) or in a general practice (AOR 1.9) versus a sexual health clinic; and monthly or greater use of benzodiazepines (AOR 2.8).

Pharmacokinetic and pharmacodynamic interactions

Of the 392 participants on a concomitant medication, 17 (4.3%) participants (3.3% of all participants) were taking a concomitant medication contraindicated with their ART. Contraindicated combinations detected were ritonavir (budesonide, fluticasone, meloxicam, quetiapine, rivaroxaban, simvastatin), darunavir (salmeterol), rilpivirine (esomeprazole, omeprazole, pantoprazole), atazanavir (esomeprazole, fluticasone, pantoprazole, quetiapine, rabeprazole, rivaroxaban, simvastatin), lopinavir (fluticasone)

Table 2. Polypharmacy of concomitant medications.

Covariate[a]	Polypharmacy							
	Yes	No	OR	95% CI	*P* value	AOR	95% CI	*P* value
Socio-demographic								
Male	120	373	4.3	1.0–18.5	0.031			
>51 Years old	89	183	3.2	2.0–5.0	<0.001			
Australian born	87	234	1.8	1.1–2.7	0.011			
Australian citizen	117	343	3.9	1.5–9.9	0.002			
Lives alone	66	145	2.1	1.4–3.1	<0.001			
Not in a relationship	87	211	2.2	1.4–3.5	<0.001			
Not currently in a sexual relationship	84	218	1.8	1.2–2.8	0.005			
English spoken at home	121	371	9.5	1.3–70.2	0.008			
Self-rated ability to read, speak and understand English as 'below average/poor'	6	7	2.9	1.0–8.8	0.049			
Uses NGO/community outreach for assistance in HIV care in last 12 months	30	47	2.5	1.5–4.0	<0.001			
Finances and employment								
No private health insurance	83	218	1.8	1.2–2.7	0.008			
Lives in subsidized housing	41	63	2.7	1.7–4.3	<0.001			
Income from social welfare	81	131	4.1	2.6–6.2	<0.001			
Not working	82	144	3.6	2.3–5.5	<0.001			
Required financial assistance/support for necessities (e.g. food, rent, household bills), over previous 12 months	49	88	2.4	1.5–3.7	<0.001			
Went without necessities for financial reasons, over previous 12 months	35	79	1.6	1.0–2.6	0.036			
Required financial assistance for government subsidized/ nonsubsidized pharmaceuticals/disorder testing	57	89	3.1	2.0–4.7	<0.001			
Not paying to see general practitioner (e.g. GP bulk bills)	62	90	3.4	1.7–7.1	0.001			
Not spending money on any HIV services (e.g. no out-of-pocket HIV services cost)	75	212	1.7	1.1–2.6	0.029			
Spending less than the sample median for ART costs	73	192	1.7	1.1–2.6	0.015			
Spending more than the sample median on concomitant medication costs	73	175	2.3	1.5–3.5	<0.001			
Reached the Medicare Safety Net in the previous 12 months[b]	50	80	2.8	1.8–4.3	<0.001			
Physical health								
Diagnosed comorbidity	103	189	6.3	3.7–10.7	<0.001	4.2	2.0–8.6	<0.001
Not being diagnosed with an STI in the previous 12 months	112	339	2.2	1.1–4.7	0.027			
Previous AIDS	45	75	2.5	1.6–4.0	<0.001			
Self-rated health as poor	29	59	1.8	1.1–3.0	0.020			
≥1 Overnight hospitalization in the previous 12 months	35	73	1.8	1.1–2.9	0.013			
Estimated glomerular filtration rate <60 ml/min per 1.73 m^2	23	20	4.4	2.3–8.4	<0.001	3.8	1.5–10.1	0.006
Delayed or interrupted concomitant medications in the previous 12 months	24	36	2.0	1.2–3.6	0.013			
Delayed or interrupted concomitant medications prior to 12 months ago	20	29	1.9	1.0–3.5	0.044			
Mental health								
Major depressive disorder	30	57	2.0	1.2–3.2	0.007			
Drug use (at least monthly)								
Benzodiazepines ('benzos')	21	18	4.4	2.3–8.6	<0.001	2.8	1.1–7.7	0.035
Steroids	8	4	6.9	2.1–23.5	<0.001			
Opiates	7	4	6.1	1.7–21.0	0.001			
HIV healthcare and treatment access								
HIV managed by a hospital based clinic[c]	72	182	1.7	1.1–2.6	0.009	2.0	1.0–3.6	0.030
HIV managed in a general practice[c]	63	111	2.8	1.8–4.2	<0.001	1.9	1.0–3.7	0.038
Accessed hospital-based pharmacy	78	181	2.1	1.4–2.5	<0.001			
Receiving care from primary HIV physician for longer than the sample mean (>10 years)	88	178	3.2	2.0–5.0	<0.001			
Other specialist(s) involved in care	95	226	2.7	1.7–4.3	<0.001			
Other healthcare providers involved in HIV care/treatment	92	232	2.2	1.4–3.5	0.001			
Enrolled in a randomized clinical trial	16	29	1.9	1.0–3.7	0.040	3.5	1.3–9.0	0.011
Diagnosed with HIV pre-2010	114	318	4.1	1.9–92	<0.001			
ART regimen, side effects, consistent use, adherence								
Commenced ART prior to 2004	87	160	4.2	2.6–6.6	<0.001			
Protease-inhibitor containing regimen	57	134	1.8	1.2–2.7	0.006			
ART side effects	79	218	1.5	1.0–2.3	0.045			
>1 ART tablet per day	99	262	2.3	1.4–3.9	0.001			
More than once-daily ART dosing	59	127	2.0	1.3–3.1	0.001			
More than 1 year undetectable HIV viral load	103	296	2.0	1.1–3.4	0.016			
Stops taking ART when feeling worse	17	31	1.9	1.0–3.6	0.039			

AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; GP, general practitioner; NGO, non-governmental organization; OR, odds ratio; STI, sexually transmitted infection.

[a]Spending more than the sample mean on concomitant medications was intentionally removed from modelling, due to the linear relationship between more medications and increased spending.

[b]Whereby there is no out-of-pocket/'gap' payment for GP services above the Medicare standard rebate.

[c]Versus a sexual health clinic/centre.

and saquinavir (budesonide, citalopram, sildenafil, tadalafil).

Five of the 17 participants took two contraindicated combinations, and one took four contraindicated combinations.

In total, 730 ART-concomitant medication combinations in 237 (60.5%) of the 392 participants were identified as having a potential for DDI. These were most commonly related to protease inhibitor use. For example, 223 combinations existed between ritonavir and concomitant medications [e.g. ritonavir with rosuvastatin (29 occurrences), atorvastatin (15 occurrences), mirtazapine (13 occurrences), oxycodone (two occurrences) or sildenafil (eight occurrences)]; and 115 combinations with darunavir [e.g. darunavir with diazepam (eight occurrences), budesonide/formoterol (two occurrences) or rosuvastatin (15 occurrences)]. From drug classes other than protease inhibitors, efavirenz contributed 83 potential DDIs. For over-the-counter concomitant medications, the most common interactions identified were between integrase inhibitors and supplements containing magnesium or calcium [27 (4% of total DDI combinations)].

Polypharmacy, pharmacokinetic and pharmacodynamic interactions taken together

Two hundred and eighty (53.6%) participants had at least one of polypharmacy, pharmacokinetic/pharmacodynamic interaction or contraindication (Supplementary Table 4, http://links.lww.com/QAD/B185).

Adverse effects and concomitant medication use or polypharmacy

Adverse symptoms were reported by 178 (34.1%) participants, most commonly sleep disturbance [156 (29.9%)], diarrhoea [135 (25.8%)] and nausea [110 (21.1%)]. Concomitant medication use was significantly associated with sleep disturbance [odds ratio (OR) 2.6, 95% confidence interval (CI) 1.5–4.2, $P < 0.001$], lipodystrophy (OR 6.0, 95% CI 2.2–17.0, $P < 0.001$) and myalgia (OR 2.1, 95% CI 1.1–3.9, $P = 0.019$). Polypharmacy of concomitant medication was significantly associated with diarrhoea (OR 1.6, 95% CI 1.0–2.4, $P = 0.046$), lipodystrophy (OR 2.4, 95% CI 1.4–4.1, $P = 0.001$), fatigue (OR 1.7, 95% CI 1.1–2.6, $P = 0.015$), myalgia (OR 1.7, 95% CI 1.0–2.9, $P = 0.033$) and peripheral neuropathy (OR 3.9, 95% CI 2.4–6.4, $P < 0.001$).

In bivariate analyses, a higher Charlson index score was associated with the adverse effects of lipodystrophy ($P = 0.001$) and peripheral neuropathy ($P < 0.001$), but not with any of the other adverse effects reported. When adjusted for disease burden (using the Charlson index score), polypharmacy remained significantly associated with diarrhoea (AOR 1.9, 95% CI 1.1–3.0, $P = 0.013$), fatigue (AOR 1.7, 95% CI 1.0–2.6, $P = 0.032$) and peripheral neuropathy (AOR 3.1, 95% CI 1.8–5.2, $P \leq 0.001$). Higher comorbid disease burden was significantly associated with lipodystrophy (AOR 1.2, 95% CI 1.1–1.5, $P = 0.012$), and neither polypharmacy nor disease burden were statistically significantly associated with myalgia in the adjusted model.

Concomitant medication adherence

Of the 392 participants on concomitant medications, 60 (15.3%) reported missed doses in the previous 12 months, of which 37 (61.7%) interrupted their concomitant medications for at least 1 week. This was a higher proportion than those who self-reported missing ART for greater than or equal to a week in the same period [20 participants (3.8%)] (Supplementary Table 5, http://links.lww.com/QAD/B185).

Results of the bivariate analyses of concomitant medication adherence are shown in Table 3. Four covariates were independently associated with imperfect concomitant medication adherence requiring financial support (AOR 27.8), foregoing necessities for financial reasons (AOR 11.1), good or very good self-reported health (AOR 14.1) and at least 1 bed day for illness in the previous 12 months (AOR 14.0).

Discussion

In this sample of HIV-infected Australian adults, 75% took a concomitant medication, and 54% of participants had one or more of polypharmacy (23%), pharmacokinetic or pharmacodynamic interaction (45%) or contraindication (3%). Over 700 potential DDIs were identified. Sixty (11.5%) reported imperfect concomitant medication adherence. Multiple adverse symptoms were more common in those taking concomitant medication.

Over 90% of patients taking a concomitant medication took at least one prescribed concomitant medication, but many were also on complementary/alternative medication and over-the-counter preparations. Patient disclosure of over-the-counter or complementary therapy usage is often underestimated [39]. One meta-analysis of 40 studies investigating complementary medicine use in HIV-infected adults found an average of 60% of patients use complementary medications – more likely in MSM, nonminority, better educated and less impoverished patients [39].

In our sample, financial barriers were associated with imperfect adherence to concomitant medications, whether this more specifically related to complementary medicines is unknown.

Table 3. Adherence to concomitant medications.

Covariate	Concomitant medication interruption		OR	95% CI	*P* value	AOR	95% CI	*P* value
	Yes	No						
Sociodemographic								
Not in a relationship	44	206	2.2	1.2–4.0	0.011			
Currently in a sexual relationship	43	213	1.9	1.0–3.4	0.041			
Self-rated ability to read, speak and understand English as 'below average/poor'	4	5	5.2	1.4–20.0	0.008			
Receives less social support than would like/required	44	218	1.9	1.0–3.5	0.036			
Participates in a NGO/community outreach for assistance in HIV management – as an active participant in previous 12 months	29	88	3.0	1.7–5.2	<0.001			
Finances and employment								
No private health insurance	47	204	2.9	1.5–5.6	0.001			
Lives in subsidized housing	21	73	2.2	1.2–3.9	0.008			
On social welfare	40	149	3.0	1.7–5.3	<0.001			
Unemployed	38	157	2.4	1.4–4.3	0.002			
Required financial assistance/support for necessities (e.g. food, rent, household bills), over the previous 12 months	35	87	4.5	2.6–8.0	<0.001	27.8	1.8–440	0.018
Went without necessities for financial reasons, over the previous 12 months	26	75	3.0	1.7–5.3	<0.001	11.1	1.9–114	0.042
Paid less than sample mean for ART (last time obtained)	40	186	1.9	1.1–3.5	0.026			
Physical health								
At least one comorbidity or SNAE	49	213	3.2	1.6–6.3	0.001			
Concomitant medication daily pill burden greater than the sample mean	39	178	2.0	1.1–3.5	0.017			
Delayed or interrupted concomitant medications prior to 12 months ago	38	11	66.0	28.8–151.4	<0.001			
Good/very good self-reported general health	29	50	6.0	3.3–10.7	<0.001	14.1	1.4–141	0.025
≥1 Bed day for illness in previous 12 months	44	198	2.5	1.3–4.6	0.004	14.0	1.2–163	0.035
More than one doctors visit due to illness in the previous 12 months	47	255	2.6	1.2–5.7	0.013			
Mental health								
Major depressive disorder	26	54	4.5	2.5–8.0	<0.001			
Life stressors								
Two or more major stressful events in previous 12 months	36	83	5.2	3.0–9.2	<0.001			
Drug use (at least monthly)								
Cigarettes	32	88	3.6	2.1–6.4	<0.001			
Marijuana	20	59	2.6	1.4–4.8	0.001			
Benzodiazepines ('benzos')	11	25	3.1	1.4–6.7	0.003			
Opiates	4	6	4.3	1.2–15.8	0.016			
HIV disclosure and stigma since HIV diagnosis								
Been made to feel ashamed for having HIV	39	157	2.5	1.4–4.4	0.001			
Been made to feel blamed for having HIV	29	120	1.9	1.1–3.4	0.017			
Been made to feel avoided for having HIV	38	145	2.7	1.5–4.7	<0.001			
Been made to feel awkward for having HIV	41	175	2.4	1.3–4.3	0.003			
HIV healthcare and treatment access								
HIV managed by a health centre specialized in HIV care	24	91	2.0	1.2–3.6	0.013			
HIV managed by a community based general practitioner	33	125	2.4	1.4–4.1	0.002			
Accessed hospital-based pharmacy	39	183	1.9	1.1–3.3	0.027			
Requires home or community care services	7	6	8.0	2.6–24.7	<0.001			
Accessed HIV-related community organization or peer support groups in management of HIV	18	49	2.8	1.5–5.2	0.001			
Receiving care from primary HIV physician for <10 years	35	152	1.9	1.1–3.4	0.019			
Other specialist(s) involved in care	47	231	2.2	1.1–4.1	0.018			
No other healthcare specialists/workers involved in HIV care/treatment	48	232	2.4	1.2–4.6	0.010			
Sees a physiotherapist and does not pay	7	8	10.5	1.1–102.5	0.023			
Greater than one missed appointment in the previous 12 months	15	39	2.8	1.4–5.5	0.002			

Table 3 (*continued*)

Covariate	Concomitant medication interruption		OR	95% CI	*P* value	AOR	95% CI	*P* value
	Yes	No						
Felt not at all informed about ART's impact on lifestyle when first started ART	26	107	1.8	1.1–3.2	0.030			
When first started ART felt not at all informed or only somewhat informed on all of: side effects, benefits, dosage requirements, impact on lifestyle, own regimen	10	29	2.3	1.1–5.0	0.032			
When starting ART, main reason was to prevent transmission to partners uninfected with HIV	17	58	2.2	1.1–4.0	0.015			
When starting ART, main reason was to prevent transmission to others uninfected with HIV in the community	17	51	2.5	1.3–4.7	0.004			
When starting ART, main reason was due to high viral load	39	154	2.7	1.5–4.8	0.001			
When starting ART, main reason was due to low $CD4^+$ cell count	39	186	1.9	1.0–3.4	0.020			
When starting ART, main reason was following own request	13	41	2.2	1.1–4.5	0.020			
ART regimen, side effects, consistent use, adherence								
Sometimes forgets to take ART	41	157	2.9	1.6–5.2	<0.001			
Careless at times about taking ART	18	59	2.3	1.2–4.2	0.009			
Stops taking ART when feeling worse	15	29	3.9	1.9–7.8	<0.001			
In the last week, has not taken ART (at least once)	21	50	3.4	1.9–6.3	<0.001			
In the past weekend, has missed ≥3 ART doses	20	50	3.2	1.7–5.9	<0.001			
In the past 12 months, delayed or interrupted ART	16	12	10.8	4.8–24.4	<0.001			
Prior to 12 months ago, delayed or interrupted ART	23	49	4.4	2.4–8.0	<0.001			
Has had ART side effects in previous 12 months	47	205	2.9	1.5–5.5	0.001			
Delayed or interrupted concomitant medications prior to 12 months ago	38	11	66.0	28.8–151.4	<0.001			
ART-related necessity concerns								
Necessity concerns score, lower necessity beliefs than sample	39	164	2.3	1.3–4.1	0.003			
Quality of life								
PROQOL-HIV, lower quality of life than sample	45	150	4.4	2.4–8.1	<0.001			

AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; NGO, non-governmental organisation; PROQOL-HIV, patient reported outcomes quality of life - HIV; SNAE, serious non-AIDS event.

Participants also self-reported taking prescription medications recreationally, as well as other classes of recreational drugs at similar rates to other Australian surveys [40].

The mean age of our cohort was 51 years, and over half (56%) had at least one known comorbidity. This is consistent with other cohorts that have found at least one comorbidity in 58 [41] to 70% [42] of HIV-infected patients over 50 years of age. Noncommunicable diseases, and multiple conditions at once, are more common in HIV-infected adults than in the general population [41,43], and increase with age [42]. In fact in one study, the prevalence of at least two noncommunicable diseases in HIV-infected adults across all age groups was similar to the prevalence of those 10 years older in the general population [41]. In our cohort, polypharmacy was independently associated with a low eGFR and a diagnosed comorbidity/SNAE; these findings support the literature reporting that the likelihood of polypharmacy increases with age [4], and the high proportion of concomitant medications and polypharmacy in our cohort is not surprising given the high rates of comorbid conditions.

HIV care at a hospital-based clinic or a general practice site also independently associated with polypharmacy; those managed at a sexual health clinic/service may have fewer chronic medical needs (or alternatively the need for concomitant medications was less well scrutinized). Clinical trial participation was also significantly associated with polypharmacy. Patients who are selected for clinical trial participation may be more engaged in care, compliant, motivated or health-seeking, thereby also more likely to initiate and remain on a concomitant medication.

The only recreational drug class to maintain significant association with polypharmacy was benzodiazepines. Participants self-reported nonprescribed benzodiazepine use with other commonly used recreational drugs, and participants may have over-reported (providing detail regarding prescribed use).

Given that ART usually consists of three antiretroviral agents (either individually or coformulated), our definition of polypharmacy was conservative, as participants defined as having polypharmacy were in fact mostly taking at least eight medicines [4]. Had we included antiretroviral medications in our definition of polypharmacy, the proportion taking at least five medications would be 59% (not 23%).

As pill burden (in addition to polypharmacy) is associated with nonadherence to medications in the literature, the positive gains of STRs for ART may be offset by the higher concomitant medication pill-burden, potentially reducing both ART and concomitant medication adherence. The benefit of single-tablet ART regimens might, therefore, be more effective if concomitant medications were likewise coformulated and minimized as much as possible. However, an Italian study found patients with polypharmacy were less likely to be on a single-tablet ART regimen, hypothesizing this may be a prescribing choice made due to the restricted capacity to manage drug interactions and the decision to avoid pharmacodynamic interactions caused by tenofovir disoproxil fumarate or abacavir (commonly found in coformulated ART at the time of analysis) [44]. New STRs with less likelihood for interactions are required.

Contraindicated ART-concomitant medication combinations were uncommon (3%), a similar prevalence to that found in the Swiss cohort study (2%) [6] and a large US cohort (7%) [19]. Potential DDIs were far more common, but their clinical relevance is unknown. Further work evaluating dosing modifications and clinical monitoring adjustments made to prevent or monitor DDIs, and longitudinal studies of patient outcomes would be useful to determine the clinical importance of the DDIs.

Our analysis is novel in its finding that polypharmacy of concomitant medication was significantly associated with diarrhoea, lipodystrophy, fatigue, muscle pain/weakness and peripheral neuropathy. These symptoms may represent adverse effects of ART or of concomitant medications, or may indicate use of concomitant medications to alleviate adverse effects. We adjusted for the presence and severity of comorbidities using the Charlson index, a validated measure of disease burden [45]; this index provided an objective tool to evaluate the impact of comorbidities in analysing the association between polypharmacy and adverse effects. Three of the five adverse effects remained statistically significantly associated with polypharmacy after adjustment for Charlson score: diarrhoea, fatigue and peripheral neuropathy. Although our data are unable to clarify causality, this finding is notable in that polypharmacy is associated with adverse effects even when adjusted for comorbid disease burden.

Of the above symptoms, it is perhaps more likely that lipodystrophy and neuropathy are ART related, given that they are known side effects of ART; although fatigue and myalgia may be more likely to be concomitant medication related, as these symptoms are not likely to lead directly to prescription of concomitant medication. The adverse effects examined are unlikely due to HIV *per se*, as all patients had undetectable viral loads and the vast majority (90%) had a $CD4^+$ T-lymphocyte cell count more than 350 cells/μl.

Imperfect adherence to concomitant medication was independently associated with financial burden (requiring financial support, or going without necessities for financial reasons) and overall wellness (self-reported good/very good general health, or having $\geq$1 bed day for illness in the previous 12 months). These seemingly paradoxical results suggest that participants are less likely to take their concomitant medications when they are feeling much worse or very well. Conversely, some participants might be reporting poorer health as they don't take all of their concomitant medication, or ART.

We hypothesized that participants who took concomitant medications or had polypharmacy of concomitant medications would be less adherent to their ART. In our cohort, participants were more likely to be nonadherent to concomitant medications than ART. However, in regression analysis, the association between suboptimal concomitant medication adherence and suboptimal ART adherence did not maintain significance. Furthermore, polypharmacy was not associated with suboptimal ART adherence. Others have found HIV patients to prioritize ART over concomitant medications; one small single-centre study demonstrated a higher level of necessity scores and lower concern scores for ART than concomitant medications, increasing for those patients on at least two concomitant medications [46]. Our questionnaire only assessed necessity and concern scores for ART and we are, therefore, unable to compare these with beliefs regarding concomitant medications in our cohort. However, the higher level of adherence to ART than concomitant medications may indicate participants prioritise ART over concomitant medications.

A previous analysis examined suboptimal ART adherence in this cohort [22]. The covariates independently associated with suboptimal ART adherence and with concomitant medication adherence were the socio-economic variables of financial strain in this analysis, whereas in the prior analysis, it was living in subsidized

housing. It may be participants who are under financial strain prioritize ART maintenance over concomitant medications. However, financial strain was significantly associated with both ART and non-ART adherence.

Our study has limitations. We reported on a mainly male population of HIV-infected adults enrolled in a country where medications are highly subsidized. However, the enrolled cohort is demographically representative of HIV-infected patients in Australia and other cohorts such as the Australian HIV Observational Database [23]. These results cannot necessarily be generalized to women or children, or to countries with different socio-economic contexts or without universally subsidized healthcare systems. In our sample, it is unknown which concomitant medications were interrupted. Our data are cross-sectional, so we were unable to evaluate whether any harm was incurred due to pharmacokinetic/pharmacodynamic interactions. This study did not ask for data on concomitant medication dosage, so we are unable to report on dose adjustments that might mitigate potential DDIs. In our effort to design a comprehensive study looking at a wide range of medical, socio-demographic and social variables we assessed a large number of variables that create a risk of collinearity. However, sensitivity analyses were performed to ensure key variables were consistently significant across all models.

As HIV-infected patients continue to live longer, it is important to manage concomitant medications, so that they do not cause harm or reduce ART adherence or potency. Over half of our sample had one or more of polypharmacy or drug interaction; efforts should be made to minimize polypharmacy, to develop new antiretrovirals with fewer drug interactions and to prescribe concomitant medications that do not cause side effects.

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Conflicts of interest

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