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ORIGINAL ARTICLE

What are the predictors of change in multimorbidity among people with HIV? A longitudinal observational cohort study

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Abstract

Introduction: Multimorbidity is common among people living with HIV (PLWH), with numerous cross-sectional studies demonstrating associations with older age and past immunosuppression. Little is known about the progression of multimorbidity, particularly in the setting of long-term access to antiretrovirals. This study aims to determine factors predictive of change in multimorbidity in PLWH.

Methods: People living with HIV who attended a regional HIV service were recruited to a consented observational cohort between September 2016 and March 2020. Demographic data, laboratory results and a Cumulative Illness Rating Scale (CIRS) were collected at enrolment and first clinical review of every subsequent year. Change in CIRS score was calculated from enrolment to February 2021. Associations with change were determined through univariate and multivariate linear regression.

Results: Of 253 people, median age was 58.9 [interquartile range (IQR): 51.9–64.4] years, 91.3% were male, and HIV was diagnosed a median of 22.16 years (IQR: 12.1–30.9) beforehand. Length of time in the study was a median of 134 weeks (IQR: 89.0–179.0), in which a mean CIRS score change of 1.21 (SD 2.60) was observed. Being older ($p < 0.001$) and having a higher body mass index ($p = 0.008$) and diabetes ($p = 0.014$) were associated with an increased likelihood of worsening multimorbidity. PLWH with a higher level of multimorbidity at baseline were less likely to worsen over time ($p < 0.001$).

Conclusion: As diabetes and weight predict worsening multimorbidity, routine diabetes screening, body mass index measurement, and multimorbidity status awareness are recommended.

KEYWORDS

ageing, cohort study, diabetes mellitus, HIV, models of care, multimorbidity, weight

INTRODUCTION

With widespread access to effective and safe antiretrovirals in developed countries, the vast majority of people living with HIV (PLWH) now have undetectable viral loads and decreased risk of immune deficiency [1]. Early diagnosis and access to treatment have resulted in the life expectancy of PLWH resembling that of the general population [2, 3]. Despite these improvements, PLWH continue to have worse health outcomes than the general population, with Australian hospitalization rates being 50–300% higher in PLWH [4].

There are approximately 28 000 PLWH currently living in Australia, with 21.9% of these residing in regional/rural areas [5]. PLWH in regional and remote areas are older, under greater financial stress, have decreased access to a primary care doctor for HIV management, have more frequent unplanned admissions and experience greater levels of multimorbidity than their metropolitan-based peers [5–7]. Multimorbidity is commonly defined as the presence of more than one health condition in the same individual, and in the context of HIV would be in addition to their HIV diagnosis [8]. The prevalence of multimorbidity in the general population is 20–25%, in comparison to 28–46% in PLWH [1, 6, 9–13]. PLWH have been shown to accumulate morbidities at a younger age, with the most common being asthma, cardiovascular disease and osteoarthritis [1, 3, 5, 11, 14]. The most common conditions in PLWH in Australia are anxiety, depression, asthma, metabolic disease and osteoarthritis [5], with similar trends seen in other developed countries with the addition of kidney and hepatic disease [1, 11, 14]. An increase in the burden of multimorbidity has been shown to greatly decrease quality of life, increase the financial cost of healthcare, and increase mortality in those affected [8]. Treatment goals of the Global AIDS strategy set '95-95-95' targets to have 95% of PLWH aware of their status, receive treatment and achieve viral suppression by 2030 [15]. A fourth target pertaining to quality of life, such as reducing the level of multimorbidity, has been adopted at a country level [5].

The factors associated with development of multimorbidity in PLWH are well established through cross-sectional studies [10, 14, 16–18], and models have been created to hypothesize changes in multimorbidity [19, 20], although there remains a lack of longitudinal data in understanding multimorbidity change in PLWH. The most reported association with the development of multimorbidity in the general population is age, with the established notion that as people age they accumulate additional morbidities [8, 21]. Similarly, age is associated with multimorbidity in PLWH, with those aged 50–64 years self-reporting the worst level of quality of life and experiencing the greatest level of morbidity [5, 22]. Along with age, the main variables associated with multimorbidity development in PLWH in developed countries are sex, race, body mass index (BMI), HIV virulence, antiretroviral use and time on medication [1, 10, 14, 16–18, 23].

Despite the research on associations with developing multimorbidity, we know little about what variables may influence multimorbidity over time in PLWH, with only one longitudinal study identified in an urban Brazilian context [18]. Age, AIDS diagnosis and nadir CD4 count < 200 cells/μL were reported as predictors of worsening multimorbidity over time in this study which followed a cohort for a median of 3.9 years from the date of HIV diagnosis [18]. In Australia there are no studies of multimorbidity change in PLWH and the only study is of middle-aged Australian women [24]. The objective of this study was to determine the variables that predict a change in the level of multimorbidity over time in PLWH who attended a regional HIV service in Australia.

METHODS

Setting

This observational, cohort study was conducted in Northern New South Wales (NSW) with PLWH attending the Sexual Health Services (SHS) for specialist HIV care. Northern NSW Local Health District is a geographical area ranging from Tweed Heads in the north, to Tabulam and Urbenville in the west and Grafton in the south [25]. It comprises an area of 20 732 km^2 with a population estimate of over 300 000 [25]. The area is home to 532 PLWH who are actively treated with antiretrovirals, the majority of whom receive antiretrovirals prescribed by the SHS [26]. Through the SHS, PLWH are able to access specialist care, nursing and social work support [27]. There are few primary care providers that are able to prescribe antiretrovirals in the area [28].

Participants

During routine appointments from September 2016 to March 2020, PLWH were offered the opportunity to participate in this study. Recruitment was voluntary, and open to all PLWH who had specialist HIV care through the SHS. Potential participants were provided with an information sheet, and informed consent was obtained. At recruitment, participants were given a short questionnaire of which medical practitioners were involved in their care. Model of care was defined as shared care if a primary care doctor was mostly or equally involved in

care, and specialist-only care if all or almost all care was from the HIV service.

Variables

Since 2012, all PLWH had a routine annual comprehensive health review that included an assessment of multimorbidity. In addition to blood pressure, weight, relevant physical exams and recommended monitoring blood tests, including CD4 count and viral load [29], all body systems were reviewed. This allowed for integrated healthcare with an opportunity to measure the level of multimorbidity in PLWH through the use of a validated tool, the Cumulative Illness Rating Scale (CIRS) [30]. The CIRS is a non-HIV-specific multimorbidity scoring tool which rates 14 body systems on a scale utilizing a published guideline [30, 31]. The scale ranges from a score of 0, reflecting the absence of disease in that body system, to 4, being system failure such as renal failure. Addition of the system scores generates an overall CIRS score which can potentially range from 0 to 56. All chronic diseases present can be included in the CIRS within the relevant body system; however, each system is only scored for the most severe condition present, and multiple conditions within one body system are not summed. There is no predefined condition list, making CIRS more comprehensive and inclusive than many multimorbidity measures [31]. A CIRS scoring guide and worksheet have been developed for PLWH and has been utilized at the service since 2012 [6]. CIRS scores were obtained for the cohort in the majority of annual SHS visits through objective assessment by their treating physician. The treating physician had access to the CIRS scoring guide, and all previous CIRS worksheets. To ensure consistency, benchmarking of CIRS assessments was conducted between the two principal assessors. Among PLWH in Australia, CIRS has been shown to be associated with age and past AIDS [6] and to predict unplanned admission [7].

The remaining data were obtained through routine clinical care including historical data contained in the clinic database. This included date and country of birth, date of HIV diagnosis, viral load, nadir CD4 count, presence of previously defined chronic health conditions [6], smoking status, drug and alcohol usage, current antiretrovirals and total number of all medications. Gender was recorded as gender identity at the time of recruitment. BMI was calculated from recorded height and weight at recruitment, or, for those with no recorded height ($n = 33$), the median value was used to estimate BMI.

Data were input into the clinic database by the treating physician after routine visits. All participant records were quality-checked by the research team and any missing data extracted from contemporaneous paper or electronic records, meaning missing data for the analysis were restricted to heights.

Data analysis

In July 2021 the data were extracted and de-identified. Participant names were removed and dates of birth were converted to age in years as of extraction date. Continuous variables were assessed for normality through a Shapiro–Wilk test, and descriptive statistics were used to determine mean and standard deviation for those that were normally distributed, and median and interquartile range (IQR) if not.

For this analysis the outcome variable of interest was change in CIRS score. This was calculated by subtracting the CIRS score at recruitment from the last CIRS score prior to data extraction, resulting in a follow-up period of 644 person-years. In order to decrease the burden on trial participants, CIRS questionnaires were typically completed during their first routine of the year, regardless of when they were entered into the study. Those without a baseline or second CIRS scores were excluded from the analysis. We compared key demographics between those included and excluded from the analysis. Comparison was by *t*-tests for means, Wilcoxon rank sum for medians and χ^2 test for categorical variables. Age was reported as medians within the results and as mean in Table 2 for the inclusion in the regression as it was normally distributed.

The dependent variable of interest was the time series change of CIRS scores measured between the first and last questionnaire. Predictor variables comprised time-point data such as age at last follow-up, BMI at recruitment, model of care and presence of defined disease at recruitment; time-series data such as change to antiretrovirals or viral load during follow-up; and demographic data such as sex, ever diagnosis of defined disease, ever defined antiretroviral use and nadir CD4 count. Associations with change in CIRS score for all predictor variables were determined through univariate linear regression. All variables with a significance level of 0.05 or less were included in a multivariate linear regression to determine the best prediction model of multimorbidity. As the recruitment period lasted 3.5 years, length of time in the study varied, and so it was included a priori in the multivariate analysis to prevent potential confounding. Analysis was conducted on SPSS [32].

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement Guidelines were used in the reporting of this observational cohort study [33]. Ethics approval was obtained from North Coast Human Ethics Research Committee (approval no. LNR143) prior to the commencement of the study.

RESULTS

Of the 332 recruited to the study, one withdrew and 17 did not have a baseline CIRS score recorded. Of the 314 remaining, 61 did not have a second CIRS score recorded, of whom 10 died, 25 had confirmed transfer of care, eight were lost to follow-up and 18 remained in care (Figure 1). The 78 excluded from the study were younger [median age 52.6 years (IQR: 46.7–60.3) vs 58.9 years (IQR: 51.0–64.4), $p < 0.001$], had a shorter duration of HIV [mean 18.3 years (SD 10.5) vs 21.6 years (SD 10.5), $p = 0.014$] and had a lower median recruitment CIRS score [6 (IQR: 3–9) vs 7 (IQR: 4–10), $p = 0.022$]. They were otherwise similar to the included cohort (Table 1). Those who died had a median CIRS score of 8.5 (IQR: 6–10) but were of a similar age to those included in the analysis. No participants were recorded as deceased after a second CIRS score but within the study period. Lack of second CIRS score for those remaining in care and missed recruitment was primarily due to time constraints of consultations; refusal was not formally documented but was minimal. Overall CIRS score by age bracket is shown in Table 2.

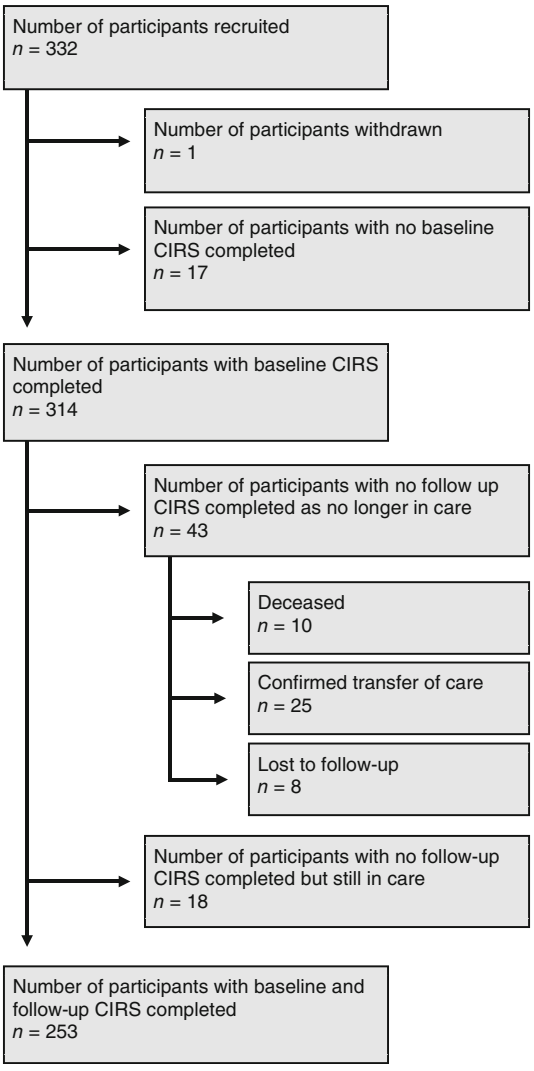

FIGURE 1 Flowchart of participants through the follow-up period

The change in CIRS score analysis was conducted for the 253 participants with a second CIRS score (Table 3). This cohort was reflective of regional PLWH; the majority were male (91.3%), had a median age of 58.9 years (IQR: 51.9–64.4), were born in Australia (82.6%), were first diagnosed a median 22.16 years ago (IQR: 12.1 to 30.9) and had a mean BMI of 25.3 (SD 4.1). Most (74.7%) of the cohort had ever used tobacco. Model of care was evenly split between shared care with a primary care doctor and HIV specialist (49.8%) and HIV specialist only (50.2%). Of the cohort, 32.0% had a nadir CD4 count < 200 cells/μL, and 85.8% maintained a viral load < 50 copies/mL from recruitment. AIDS had ever been diagnosed in 17.8%, and hepatitis C had ever been diagnosed in 14.6%. Use of antiretrovirals revealed 70.0% had been exposed to tenofovir disoproxil fumarate (TDF), and 21.7% to zidovudine. A change in antiretroviral therapy since recruitment occurred in 72.7% of the cohort, and the median number of all antiretroviral and non-antiretroviral medications taken by participants at recruitment was 4 (IQR: 2.0–6.0).

Median CIRS score at recruitment was 7 (IQR: 4.0–10.0), with a median of 4 different body systems affected (IQR: 3.0–6.0). Median time in the study was 134 weeks (IQR: 89.0–179.0). Mean CIRS score change for all participants was 1.21 (SD 2.60) and was normally distributed as tested by Shapiro–Wilk, with 69.4% of participants having a CIRS score change of between −2 and +2 points (Figure 2).

In the univariate analysis (Table 3), factors associated with change in CIRS score were age ($B = 0.330$, $p = 0.029$), nadir CD4 count < 200 cells/μL ($B = -0.902$, $p = 0.010$), recruitment CIRS score ($B = -0.126$, $p = 0.001$), BMI ($B = 0.106$, $p = 0.008$), antiretroviral change ($B = 0.761$, $p = 0.038$) and a diabetes mellitus (diabetes) diagnosis at recruitment ($B = 1.781$, $p = 0.026$). The multivariate analysis (Table 4) found that age ($B = 0.054$, $p \leq 0.001$), BMI at recruitment ($B = 0.100$, $p = 0.008$) and diabetes diagnosis at recruitment ($B = 1.835$, $p = 0.014$) predicted a worsening CIRS score by the time of follow-up, while keeping all other variables constant. A higher recruitment CIRS score ($B = -0.185$, $p \leq 0.001$) predicted a decline in follow-up CIRS score. For an increase of one point in participants' recruitment CIRS score, follow-up CIRS scores are predicted to decline by 0.185 points. Change to antiretroviral therapy ($B = 0.335$, $p = 0.332$) and nadir CD4 count < 200 cells/μL were not statistically significant in the multivariate

TABLE 1 Baseline demographics of all participants, comparing those who were included in the final analysis and those excluded due to lack of follow-up Cumulative Illness Rating Scale (CIRS) score

	Total ($n = 331$)	Included ($n = 253$)	Excluded/without follow-up CIRS score ($n = 78$)	p[a]
Age as of 01 March/21 years [median (IQR)]	**57.5 (49.2–63.1)**	**58.9 (51.9–64.4)**	**52.6 (46.7–60.3)**	**<0.001**
Gender [n (%)]				
Male	307	231 (75.2)	76 (24.8)	0.068
Female	24	22 (91.7)	2 (8.3)	
Country of birth [n (%)]				
Australia	270	209 (77.4)	61 (22.6)	0.381
Other	61	44 (72.1)	17 (27.9)	
Duration of HIV at 1 March/21 years [mean (SD)]	**20.8 (10.6)**	**21.6 (10.5)**	**18.3 (10.5)**	**0.014**
Recruitment CIRS score [median (IQR)]	**7 (4–10)**	**7 (4.0–10.0)**	**6 (3–9)**	**0.022**
Tobacco use [n (%)]				
Never	80	64 (80.0)	16 (20.0)	0.518
Ever	247	189 (76.5)	58 (23.5)	
Ever AIDS diagnosis [n (%)]				
No	275	208 (75.6)	67 (24.4)	0.448
Yes	56	45 (80.4)	11 (19.6)	
Ever Hep-C diagnosis [n (%)]				
No	280	216 (77.1)	64 (22.9)	0.477
Yes	51	37 (72.5)	14 (27.5)	
Model of care [n (%)]				
Shared care	170	126 (74.1)	44 (25.9)	0.307
Specialist only	161	127 (78.9)	34 (21.1)	
Pharmacotherapy [n (%)]				
Any exposure to zidovudine	66	55 (83.3)	11 (16.7)	0.140
Any exposure to tenofovir disoproxil fumarate	230	177 (77.0)	53 (23.0)	0.736

Note: Bold has been used for variables with $p < 0.05$.
[a]t-tests for means, Wilcoxon rank sum for medians and χ^2 test for categorical variables.

TABLE 2 Number Cumulative Illness Rating Scale (CIRS) score recorded at baseline and last follow-up by age group

Age group (years)	No. of participants recruited	No. of participants with baseline CIRS score	No. of participants with follow-up CIRS score	Median baseline CIRS score (IQR)	Range
0–29	5	5	4	5 (3–6)	1–6
30–39	26	24	13	3 (1.5–4.5)	0–9
40–49	54	51	40	5 (3–7)	0–20
50–59	110	107	81	7 (4–9)	1–18
60–69	108	99	89	9 (5–11)	2–21
70–100	28	28	26	10.5 (8–12)	2–20

analysis. All results were controlled for length of time in study. The incidence of predefined disease was found to increase in all diseases, with the most prevalent being vascular disease and the largest change detected in renal disease (Table 5).

DISCUSSION

This study represents the first effort to examine the change in multimorbidity in PLWH over time in an Australian context, and only the second globally.

TABLE 3 Univariate analysis of predictors of mean change in Cumulative Illness Rating Scale (CIRS) score. A univariate linear regression model was used to analyse the relationship between each predictor and mean CIRS score change

	Total ($n = 253$)	Mean CIRS score change (SD)	*B*	SE	*p*
Age as of 01 March/21 years [mean (SD)]	**57.4 (10.9)**	**1.21 (2.60)**	**0.330**	**0.150**	**0.029**
Gender [*n* (%)]					
Male	231 (91.3)	1.21 (2.599)	0.026	0.582	0.964
Female	22 (8.7)	1.18 (2.702)			
Country of birth [*n* (%)]					
Australia	209 (82.6)	1.25 (2.595)	−0.249	0.432	0.565
Other	44 (17.4)	1.0 (2.659)			
Duration HIV at 01 March/21 years [median (IQR)]	22.16 (12.1–30.9)	1.21 (2.60)	0.025	0.016	0.115
Nadir CD4 cell count [*n* (%)]					
≤200 cells/μL	**81 (32.0)**	**0.59 (2.774)**	**−0.902**	**0.349**	**0.010**
>200 cells/μL	**172 (68.0)**	**1.49 (2.474)**			
Viral load since recruitment [*n* (%)]					
≤50 copies/mL	217 (85.8)	1.20 (2.581)	0.052	0.469	0.912
>50 copies/mL	36 (14.2)	1.25 (2.771)			
Medications at recruitment [median (IQR)]	4 (2.0–6.0)	1.21 (2.60)	0.028	0.047	0.555
Recruitment CIRS score [median (IQR)]	**7 (4.0–10.0)**	**1.21 (2.60)**	**−0.126**	**0.039**	**0.001**
CIRS systems affected at recruitment [median (IQR)]	4 (3.0–6.0)	1.21 (2.60)	−0.068	0.043	0.117
BMI at recruitment [mean (SD)]	**25.3 (4.1)**	**1.21 (2.60)**	**0.106**	**0.040**	**0.008**
Tobacco use [*n* (%)]					
Never	64 (25.3)	1.19 (2.069)	0.024	0.377	0.949
Ever	189 (74.7)	1.21 (2.765)			
Mental health diagnosis at recruitment [*n* (%)]					
No	177 (70.0)	1.10 (2.396)	0.346	0.357	0.334
Yes	76 (30.0)	1.45 (3.035)			
Alcohol or other drug concern at recruitment [*n* (%)]					
No	208 (82.2)	1.28 (2.674)	−0.439	0.428	0.306
Yes	45 (17.8)	0.84 (2.236)			
Vascular disease at recruitment [*n* (%)]					
No	148 (58.5)	1.09 (2.653)	−0.267	0.332	0.422
Yes	105 (41.5)	1.36 (2.535)			
Renal disease at recruitment [*n* (%)]					
No	240 (94.9)	1.23 (2.614)	−0.541	0.742	0.467
Yes	13 (5.1)	0.69 (2.428)			
Diabetes mellitus at recruitment [*n* (%)]					
No	**242 (95.7)**	**1.13 (2.474)**	**1.781**	**0.796**	**0.026**
Yes	**11 (4.3)**	**2.91 (4.460)**			
Ever AIDS diagnosis [*n* (%)]					
No	208 (82.2)	1.18 (2.411)	0.128	0.429	0.765
Yes	45 (17.8)	1.31 (3.383)			
Ever hepatitis C diagnosis [*n* (%)]					
No	216 (85.4)	1.24 (2.586)	−0.241	0.464	0.604
Yes	37 (14.6)	1.00 (2.728)			

TABLE 3 (Continued)

	Total ($n = 253$)	Mean CIRS score change (SD)	*B*	SE	*p*
Model of care [*n* (%)]					
Shared care	126 (49.8)	1.39 (2.520)	−0.365	0.327	0.265
Specialist only	127 (50.2)	1.02 (2.680)			
Pharmacotherapy [*n* (%)]					
Any exposure to zidovudine	55 (21.7)	1.21 (2.60)	0.504	0.396	0.205
Any exposure to tenofovir disoproxil fumarate	177 (70.0)	1.21 (2.60)	−0.270	0.357	0.450
Any change to antiretrovirals since recruitment	**184 (72.7)**	**1.21 (2.60)**	**0.761**	**0.365**	**0.038**

Note: Bold has been used for variables with $p < 0.05$.

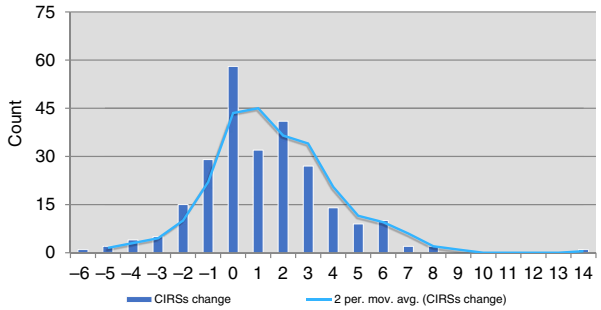

FIGURE 2 Change in Cumulative Illness Rating Scale score (CIRSs). For each participant, the change in CIRS score was calculated by subtracting the CIRSs at recruitment from the last CIRSs prior to data extraction

Increasing age, increasing BMI and having diabetes were associated with worsening multimorbidity, while having a higher baseline level of multimorbidity was protective. No HIV-related variables were associated with multimorbidity change in our cohort.

Multimorbidity change was measured through change in CIRS score, with a mean CIRS score change of 1.21 observed over a median of 134 weeks. The absence of dramatic rises in multimorbidity increase was also demonstrated in a Brazilian study [18], although this had several differences from our cohort: it followed progression of multimorbidity in newly diagnosed PLWH; recruitment date was from antiretroviral initiation; recruitment began in 2006; it had a higher proportion of female participants (33% vs 8.7%); and the mean age was lower (36.9 vs 57.4) [18]. Nevertheless, the consistency of finding minimal progression of PLWH in the current era is reassuring. In our study, a higher level of multimorbidity at recruitment was demonstrated to have a protective effect in multimorbidity change. It is possible that identification of multimorbidity by HIV specialists may motivate interventions to decrease multimorbidity, and hence routine multimorbidity measurements may have outcome benefits for PLWH.

The increase in prevalence of specific conditions demonstrates the accumulative nature of predefined conditions. A compounding effect has been demonstrated in the general population, with the presence of one disease predisposing to the accumulation of another [24, 34, 35]. The high prevalence of individual morbidities has been documented widely in PLWH [1] and has also been observed to accumulate over time [18]. The modest mean increase in CIRS score but frequent new diagnosis of specific conditions suggests that multiple factors besides predefined conditions are contributing to multimorbidity levels. These factors probably include improvement and resolution of existing health conditions through medical management occurring at the same time as development of new or worsening conditions. No negative association was found between CIRS score progression and the model of care received by the PLWH, which is reassuring for regional Australia where HIV specialists may be the only healthcare provider [5].

In a cross-sectional setting, age has been demonstrated to be associated with the onset of multimorbidity in PLWH [8, 21]. Studies from other high-income countries have also demonstrated that PLWH have an increased burden of multimorbidity compared with the age-matched general population [1, 10, 36, 37]. In our study, age is confirmed as predicting worsening morbidity, in agreement with Castilho et al.'s findings that older PLWH were more at risk of developing greater multimorbidity than their younger peers when stratified by 10-year intervals [18].

Obesity has been firmly established in the development of morbidities such as diabetes, cardiovascular disease, joint disorders, mood disorders and hypertension [16, 38–40], so it is consistent that BMI predicts worsening multimorbidity and this has been demonstrated in the general population in Australia [41]. The association between BMI and the development of multimorbidity in PLWH has been demonstrated [14, 16], with American PLWH classified as obese upon antiretroviral initiation

TABLE 4 Multivariate analysis of predictors of mean change in Cumulative Illness Rating Scale (CIRS) score. A multivariate linear regression model was created to predict CIRS score change based on the significant predictors identified in the univariate analysis. Length of time in the study was controlled for in this analysis

	Total ($n = 253$)	Mean CIRS score change (SD)	*B*	SE	*p*
Age as of 1 March/21 years [mean (SD)]	**57.4 (10.9)**	**1.21 (2.60)**	**0.054**	**0.015**	**<0.001**
Nadir CD4 cell count [*n* (%)]					
≤200 cells/μL	81 (32.0)	0.59 (2.774)	−0.612	0.334	0.068
>200 cells/μL	172 (68.0)	1.49 (2.474)			
Recruitment CIRS score [median (IQR)]	**7 (4.0–10.0)**	**1.21 (2.60)**	**−0.185**	**0.041**	**<0.001**
BMI, mean (SD)	**25.3 (4.1)**	**1.21 (2.60)**	**0.100**	**0.038**	**0.008**
Diabetes mellitus at recruitment [*n* (%)]					
No	**242 (95.7)**	**1.13 (2.474)**	**1.835**	**0.743**	**0.014**
Yes	**11 (4.3)**	**2.91 (4.460)**			
Any change to antiretroviral since recruitment [*n* (%)]	184 (72.7)	1.21 (2.60)	0.335	0.345	0.332

Note: Bold has been used for variables with $p < 0.05$.

TABLE 5 Change in specified health conditions over time. Rate of prevalence of disease is compared between recruitment and most recent Cumulative Illness Rating Scale (CIRS)

	Recruitment ($n = 253$)	Most recent CIRS ($n = 253$)	Increase in prevalence (%)
Mental health	76 (29.6)	114 (45.1)	33.30
Alcohol or other drug abuse	45 (17.8)	59 (23.3)	23.70
Vascular disease	105 (41.5)	149 (58.9)	29.50
Renal disease	13 (5.1)	27 (10.7)	51.90
Diabetes mellitus	11 (4.3)	21 (8.3)	47.60

Note: date are presented as *n* (%).

having a 1.5-fold risk of developing multimorbidity [16]. As PLWH age, they are doing so in the same obesogenic environment as the general population [16, 41], but are exposed to additional risk factors such as the use of integrase inhibitors, return to health phenomena and recent cessation of TDF, which have been shown to impact the BMI of PLWH [16, 42–44]. BMI was not explored in Castilho et al. [18]

Our study demonstrated that having a diabetes diagnosis was associated with worsening multimorbidity over time. Diabetes was not found to be a predictor of worsening multimorbidity in Castilho et al. [18], where the mean age and incidence of diabetes was considerably lower than in our cohort. Men who have sex with men (MSM) who also have HIV have significantly greater odds of developing diabetes than HIV-negative MSM, with an Australian study finding a 97% increased odds [45]. PLWH have unique risk factors for the development of diabetes, such as higher rates of previous or current hepatitis C infection, lipodystrophy and previous exposure to some protease inhibitors and nucleoside analogs [46].

Limitations of this study include the relatively short mean duration of follow-up. Analysis required a second CIRS score, and therefore a significant minority were excluded due to a variety of reasons, with the most common being transfer of care. Overall, those excluded were younger with lower recruitment CIRS score, but those who died had higher recruitment CIRS score. Due to the heterogeneity of those excluded, the impact of attrition bias is likely to be minimal. The summative nature of CIRS score allows for changes in one body system to be masked in the overall score if other systems improved. Multimorbidity scoring is highly affected by methodology. We have elected to utilize CIRS as it does not have a predefined list of conditions and is therefore more consistent than studies that use a non-standardized predefined list of chronic conditions [31]. The absence of a patient-reported level of multimorbidity is also a limitation. Participants identifying as female are represented at a level similar to that of the total Australian population of PLWH (8.7% vs 10.6%), but require greater total participant numbers to determine if sex is a predictor of CIRS score change [5].

The setting of this study was regional NSW. This population tends to be older, engage less in shared care and travel further for medical care than PLWH in metropolitan areas. The expansion of this cohort to include a greater geographical area of both metropolitan and rural services, as well as correlation with self-reported measures of quality of life would assist in confirming the external validity of these findings. Comparisons between metropolitan and rural services would also be of use, particularly for planning and delivery of future health services.

Implications

As our study found BMI and diabetes to predict increases in multimorbidity in PLWH, HIV care should address these health issues. Model of care was not associated with multimorbidity progression so the choice of care model should be informed by preferences of the affected community within resource limitations. Care models should incorporate systems to identify patients with a BMI ≥25 kg/m^2 and/or a diagnosis of diabetes as being at risk for worsening multimorbidity. Managing weight and diabetes are frequent activities in primary care, with current guidelines recommending BMI and waist circumference measurement every 2 years, and a fasting blood glucose or HbA1c every 3 years for high-risk people [47]. In Australia, PLWH are recommended to have fasting blood glucose checked at entry into care, then yearly, and BMI measured every 6–24 months [48]. There are mixed recommendations for screening and diagnosis of diabetes in PLWH, with European guidelines including HbA1c if blood glucose levels are elevated, and American guidelines not recommending HbA1c for diagnosis with a preference for random or fasting glucose only [43, 49]. There may be utility in regular HbA1c or fasting glucose screening in Australian PLWH. Poor collection of height limits accuracy of BMI calculations, and HIV care services should ensure these data are recorded. Current interventions recommend counselling of lifestyle changes, pharmacotherapy and dietician referral for the management of diabetes and BMI [43, 48], but the importance of these variables as predictors of worsening multimorbidity suggest that further intervention may be worthwhile. The use of public health campaigns specific to PLWH, population-specific exercise programmes and community-based services are possibilities for greater intervention.

Multimorbidity is likely as PLWH age, yet the protective effect of baseline CIRS score demonstrates potential benefits from measuring multimorbidity and that multimorbidity in PLWH can be effectively managed.

CONCLUSION

Multimorbidity increases over time for PLWH and diabetes, higher BMI and older age predict greater increases. Except for age, these predictors allow for a point of intervention in the medical management of PLWH to improve health outcomes.

AUTHOR CONTRIBUTIONS

MC: data curation, formal analysis, writing – original draft, writing – review and editing (lead). SH: investigation, writing – review and editing (equal). DJS: investigation, writing – review and editing (equal). KP: methodology, writing – review and editing (equal). CC: formal analysis, writing – review and editing (equal). NE: conceptualization, supplemental analysis, methodology, supervision, writing – review and editing (lead).

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The corresponding author can be contacted about availability of data used to support this report. Due to the nature of informed consent obtained for this research, data on individuals are not publicly available.

ETHICS STATEMENT

This project obtained approval from North Coast NSW Human Research Ethics Committee (HREC), approval number LNR143. Written consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

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REFERENCES

1. Maciel RA, Kluck HM, Durand M, Sprinz E. Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: a cross-sectional study. *Int J Infect Dis*. 2018;70:30-35. doi:10.1016/j.ijid.2018.02.009
2. Danforth K, Granich R, Wiedeman D, Baxi S, Padian N. Global mortality and morbidity of HIV/AIDS. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, eds. *Major Infectious Diseases*. The International Bank for Reconstruction and Development/The World Bank; 2017.
3. Marcus JL, Leyden WA, Alexeeff SE, et al. Comparison of overall and comorbidity-free life expectancy between insured adults with and without HIV infection, 2000-2016. *JAMA Netw Open*. 2020;3(6):e207954. doi:10.1001/jamanetworkopen.2020.7954
4. Falster K, Wand H, Donovan B, et al. Hospitalizations in a cohort of HIV patients in Australia, 1999-2007. *AIDS*. 2010;24(9):1329-1339. doi:10.1097/QAD.0b013e328339e245
5. Power J, Amir S, Brown G, et al. *HIV Futures 9: Quality of Life among People Living with HIV in Australia*. The Australian Research Centre in Sex, Health and Society; 2019.
6. Edmiston N, Passmore E, Smith DJ, Petoumenos K. Multimorbidity among people with HIV in regional New South Wales, Australia. *Sex Health*. 2015;12(5):425-432. doi:10.1071/SH14070
7. Edmiston N, Petoumenos K, Smith DJ. Multimorbidity, not human immunodeficiency virus (HIV) markers predicts unplanned admission among people with HIV in regional New South Wales. *Intern Med J*. 2018;48(6):706-713. doi:10.1111/imj.13733
8. Australian Institute of Health and Welfare (AIHW). Chronic Conditions and Multimorbidity. Australian Government. 2020 Accessed January 30, 2023. www.aihw.gov.au/reports/australias-health/chronic-conditions-and-multimorbidity
9. Goulet JL, Fultz SL, Rimland D, et al. Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity? *Clin Infect Dis*. 2007;45(12):1593-1601. doi:10.1086/523577
10. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. 2011;53(11):1120-1126. doi:10.1093/cid/cir627
11. Salter ML, Lau B, Go VF, Mehta SH, Kirk GD. HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users. *Clin Infect Dis*. 2011;53(12):1256-1264. doi:10.1093/cid/cir673
12. Lorenc A, Ananthavarathan P, Lorigan J, Banarsee R, Jowata M, Brook G. The prevalence of comorbidities among people living with HIV in Brent: a diverse London Borough. *London J Prim Care (Abingdon)*. 2014;6(4):84-90. doi:10.1080/17571472.2014.11493422
13. World Health Organisation (WHO). *Multimorbidity: Technical Series on Safer Primary Care*. WHO; 2016.
14. Wong C, Gange SJ, Moore RD, et al. Multimorbidity among persons living with human immunodeficiency virus in the United States. *Clin Infect Dis*. 2018;66(8):1230-1238. doi:10.1093/cid/cix998
15. Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending inequalities and getting on track to end AIDS by 2030 — a summary of the commitments and targets within the United Nations General Assembly's 2021 Political Declaration on HIV and AIDS. United Nations General Assembly. Accessed February 23, 2022. https://www.unaids.org/en/resources/documents/2022/political-declaration_summary-10-targets
16. Kim DJ, Westfall AO, Chamot E, et al. Multimorbidity patterns in HIV-infected patients: the role of obesity in chronic disease clustering. *J Acquir Immune Defic Syndr*. 2012;61(5):600-605. doi:10.1097/QAI.0b013e31827303d5
17. Benzekri NA, Sambou JF, Ndong S, et al. Prevalence, predictors, and management of advanced HIV disease among individuals initiating ART in Senegal, West Africa. *BMC Infect Dis*. 2019;19(1):261. doi:10.1186/s12879-019-3826-5
18. Castilho JL, Escuder MM, Veloso V, et al. Trends and predictors of non-communicable disease multimorbidity among adults living with HIV and receiving antiretroviral therapy in Brazil. *J Int AIDS Soc*. 2019;22(1):e25233. doi:10.1002/jia2.25233
19. Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. *Lancet Infect Dis*. 2015;15(7):810-818. doi:10.1016/S1473-3099(15)00056-0
20. Smit M, Cassidy R, Cozzi-Lepri A, et al. Projections of non-communicable disease and health care costs among HIV-positive persons in Italy and the U.S.A.: a modelling study. *PLoS One*. 2017;12(10):e0186638. doi:10.1371/journal.pone.0186638
21. Appay V, Rowland-Jones SL. Premature ageing of the immune system: the cause of AIDS? *Trends Immunol*. 2002;23(12):580-585. doi:10.1016/s1471-4906(02)02338-4
22. Vance DE, Mugavero M, Willig J, Raper JL, Saag MS. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care*. 2011;22(1):17-25. doi:10.1016/j.jana.2010.04.002
23. Bae JW, Guyer W, Grimm K, Altice FL. Medication persistence in the treatment of HIV infection: a review of the literature and implications for future clinical care and research. *AIDS*. 2011;25(3):279-290. doi:10.1097/QAD.0b013e328340feb0
24. Xu X, Mishra GD, Dobson AJ, Jones M. Progression of diabetes, heart disease, and stroke multimorbidity in middle-aged women: a 20-year cohort study. *PLoS Med*. 2018;15(3):e1002516. doi:10.1371/journal.pmed.1002516
25. New South Wales Health (NSW Health). Local health districts and specialty networks - Northern NSW. NSW. 2022. Accessed January 30, 2023 https://www.health.nsw.gov.au/lhd/Pages/nnswlhd.aspx.
26. New South Wales Health (NSW Health). NSW HIV strategy 2021–2025 - quarter 4 & annual data report 2021. NSW. 2021 Accessed January 30, 2023. https://www.health.nsw.gov.au/endinghiv/Pages/nsw-hiv-strategy-2021-2025.aspx
27. New South Wales Health (NSW Health). HIV and related programs (HARP). NSW. 2022 Accessed June 22, 2022. https://nnswlhd.health.nsw.gov.au/public-health/hiv-and-related-programs-harp/sexual-health/
28. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). ASHM prescriber map. 2022 Accessed June 07, 2022. https://ashm.org.au/prescriber-maps/
29. Lundgren JDGJ, Rockstroh JK, Furrer H. *EACS Guidelines Version 8.0 October 2015*. European AIDS Clinical Society (EACS); 2015.

30. Hudon C, Fortin M, Soubhi H. Abbreviated guidelines for scoring the Cumulative Illness Rating Scale (CIRS) in family practice. *J Clin Epidemiol*. 2007;60(2):212-212.e4. doi:10.1016/j.jclinepi.2005.12.021
31. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med*. 2012;10(2):142-151. doi:10.1370/afm.1337
32. IBM Corp. *SPSS Statistics for Windows*. IBM Corp; 2017.
33. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808. doi:10.1136/bmj.39335.541782.AD
34. Lappenschaar M, Hommersom A, Lucas PJ, et al. Multilevel temporal Bayesian networks can model longitudinal change in multimorbidity. *J Clin Epidemiol*. 2013;66(12):1405-1416. doi:10.1016/j.jclinepi.2013.06.018
35. Freisling H, Viallon V, Lennon H, et al. Lifestyle factors and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study. *BMC Med*. 2020;18(1):5. doi:10.1186/s12916-019-1474-7
36. Balderson BH, Grothaus L, Harrison RG, McCoy K, Mahoney C, Catz S. Chronic illness burden and quality of life in an aging HIV population. *AIDS Care*. 2013;25(4):451-458. doi:10.1080/09540121.2012.712669
37. Heron JE, Norman SM, Yoo J, et al. The prevalence and risk of non-infectious comorbidities in HIV-infected and non-HIV infected men attending general practice in Australia. *PLoS One*. 2019;14(10):e0223224. doi:10.1371/journal.pone.0223224
38. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638. doi:10.1056/NEJMoa021423
39. Sullivan PW, Morrato EH, Ghushchyan V, Wyatt HR, Hill JO. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000-2002. *Diabetes Care*. 2005;28(7):1599-1603. doi:10.2337/diacare.28.7.1599
40. Bogers RP, Bemelmans WJ, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med*. 2007;167(16):1720-1728. doi:10.1001/archinte.167.16.1720
41. Jackson CA, Dobson A, Tooth L, Mishra GD. Body mass index and socioeconomic position are associated with 9-year trajectories of multimorbidity: a population-based study. *Prev Med*. 2015;81:92-98. doi:10.1016/j.ypmed.2015.08.013
42. Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. *Front Endocrinol (Lausanne)*. 2018;9:705. doi:10.3389/fendo.2018.00705
43. European AIDS Clinical Society (EACS) EACS. EACS Guidelines version 11.0. 2021 Accessed January 30, 2023. https://www.eacsociety.org/guidelines/eacs-guidelines/
44. Surial B, Mugglin C, Calmy A, et al. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV: a cohort study. *Ann Intern Med*. 2021;174(6):758-767. doi:10.7326/M20-4853
45. Petoumenos K, Huang R, Hoy J, et al. Prevalence of self-reported comorbidities in HIV positive and HIV negative men who have sex with men over 55 years-the Australian Positive & Peers Longevity Evaluation Study (APPLES). *PLoS One*. 2017;12(9):e0184583. doi:10.1371/journal.pone.0184583
46. Kalra S, Kalra B, Agrawal N, Unnikrishnan AG. Understanding diabetes in patients with HIV/AIDS. *Diabetol Metab Syndr*. 2011;3(1):2. doi:10.1186/1758-5996-3-2
47. The Royal Australian College of General Practitioners (RACGP). Guidelines for preventive activities in general practice. 2016 Accessed January 30, 2023. https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines
48. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). HIV shared care and GP management plan (GPMP) guide 2021. 2021 Accessed June 07, 2022. https://www.ashm.org.au/resources/hiv-shared-care/
49. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. 2021 Accessed August 30, 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf

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