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Associations between drug and alcohol use, smoking, and frailty among people with HIV across the United States in the current era of antiretroviral treatment

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CK developed the concept proposal, HC, SR, BMW, RMN, LD, CK and JACD developed the study design, AW, ALW, MS, KC, JE, SN, WM, GC, MM, EC, KM, and MK contributed to data collection, SR with support from BMW, RMN, LD and JACD conducted analyses, HC and SR drafted the first draft of the manuscript. All authors have reviewed and approved this manuscript.

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Abstract

Objective: To examine associations between frailty and drug, alcohol, and tobacco use among a large diverse cohort of people with HIV (PWH) in clinical care in the current era.

Methods: PWH at 7 sites across the United States completed clinical assessments of patient-reported measures and outcomes between 2016-2019 as part of routine care including drug and alcohol use, smoking, and other domains. Frailty was assessed using 4 of the 5 components of the Fried frailty phenotype and PWH were categorized as not frail, pre-frail, or frail. Associations of substance use with frailty were assessed with multivariate Poisson regression.

Results: Among 9,336 PWH, 43% were not frail, 44% were prefrail, and 13% were frail. Frailty was more prevalent among women, older PWH, and those reporting current use of drugs

or cigarettes. Current methamphetamine use (1.26: 95% CI 1.07-1.48), current (1.65: 95% CI 1.39-1.97) and former (1.21:95% CI 1.06-1.36) illicit opioid use, and former cocaine/crack use (1.17: 95% CI 1.01-1.35) were associated with greater risk of being frail in adjusted analyses. Current smoking was associated with a 61% higher risk of being frail vs. not frail (1.61: 95% CI 1.41-1.85) in adjusted analyses.

Conclusions: We found a high prevalence of prefrailty and frailty among a nationally distributed cohort of PWH in care. This study identified distinct risk factors that may be associated with frailty among PWH, many of which, such as cigarette smoking and drug use, are potentially modifiable.

Keywords

Substance use; frailty; alcohol use; methamphetamine use; HIV; cigarette smoking

1. Introduction

Over the last 25 years there has been a decline in HIV-related morbidity and mortality due to antiretroviral therapy (ART)(Bosh et al., 2020; Hogg et al., 1998; Palella et al., 1998). The resulting increase in survival has been accompanied by an increase in age-related morbidity and frailty, which occurs at a higher prevalence among people with HIV (PWH) (Kooij et al., 2016). Frailty is the age-related deterioration in multiple physiological systems resulting in greater vulnerability to stressors(Clegg et al., 2013). Frailty is associated with hospitalizations, falls, mortality, and among PWH increased risk of the onset of AIDS(Akgun et al., 2014; Desquilbet et al., 2011; Desquilbet et al., 2009; Erlandson et al., 2012; Guaraldi et al., 2015; Piggott et al., 2013; Tassiopoulos et al., 2017; Verheij et al., 2020).

Frailty studies among PWH often have small sample sizes(Alvarez et al., 2020; Beanland et al., 2020; Umbleja et al., 2020; Yeoh et al., 2018; Zeballos et al., 2019) and are from the pre- or earlier ART treatment eras(Desquilbet et al., 2011; Desquilbet et al., 2009; Onen et al., 2009; Sung et al., 2020). Prior work often excluded women(Althoff et al., 2014; Desquilbet et al., 2011; Desquilbet et al., 2007; Desquilbet et al., 2009; Yeoh et al., 2018), or were limited to those willing to enroll in trials(Erlandson et al., 2017; Tassiopoulos et al., 2017; Umbleja et al., 2020), with a history of injecting drugs(Piggott et al., 2020), or above specific ages(Alvarez et al., 2020; Beanland et al., 2020; Kooij et al., 2016; Yeoh et al., 2018; Zeballos et al., 2019), rather than including a diverse clinical cohort. Few studies examined the influence on frailty of factors disproportionately impacting PWH, such as substance use that is not necessarily injected, despite the potential impacts in other vulnerable populations(Brown et al., 2013; Salem et al., 2019). Studies that simultaneously assess the intersecting impact of alcohol, tobacco, and drug use on frailty, and evaluate independent impacts of individual drugs are needed. This approach is important given that drug, tobacco, and alcohol use are potentially modifiable risk factors that can identify high-risk populations within PWH who may benefit from preventive interventions, and may be associated with premature aging or comorbidities(Bachi et al., 2017); are often correlated with each other(Crane et al., 2017; Degenhardt and Hall, 2001; Paavola et al., 2004); yet

discerning the unique contributions of each to frailty among PWH requires considering these factors simultaneously.

We investigated frailty among PWH receiving care in the current ART era by examining associations between substance use and frailty among a large, racially/ethnically and demographically diverse, well-characterized cohort of PWH in care at 7 sites across the U.S.

2. Methods

2.1 Setting

We conducted this study among PWH in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort(Kitahata et al., 2008). CNICS is a longitudinal, observational cohort of PWH who are enrolled in clinical care at eight geographically distinct HIV clinics in the US from January 1995 to the present (http://www.uab.edu/cnics/) (Kitahata et al., 2008) of which seven sites had applicable data and were included in these analyses.

2.2 Participants

All PWH ≥18 years of age who completed ≥1 clinical assessment of patient reported measures and outcomes (PROs) between 2016-2019 were included. PROs are completed as part of routine care visits at CNICS sites on a touch-screen tablet(Crane et al., 2007; Fredericksen et al., 2012). PWH who were medically unstable, appeared intoxicated, had a cognitive impairment, or did not speak English or Spanish were not asked to complete the clinical assessment(Crane et al., 2007). For PWH who completed multiple assessments, the most recent assessment through 12/31/2019 was used.

2.3 Data Sources

The CNICS data repository integrates comprehensive longitudinal data from outpatient and inpatient encounters(Kitahata et al., 2008). It captures standardized HIV-related information collected at enrollment (initial clinic visit), sociodemographic, clinical, medication, and laboratory data from each site's electronic health record and other institutional data sources. Data from clinical PRO assessments are also integrated into the data repository. The clinical assessment includes measures of alcohol use (Alcohol Use Disorders Identification Test, AUDIT-C)(Bradley et al., 2003; Bradley et al., 1998), drug use (modified Alcohol, Smoking, and Substance Involvement Screening Test, ASSIST)(Newcombe et al., 2005; 2002), tobacco use including smoking cigarettes and e-cigarettes/vaping(Cropsey et al., 2016), symptoms (HIV symptoms index)(Justice et al., 2001), physical activity (Lipid Research Clinical Questionnaire, LRCQ)(Ainsworth et al., 1993; Blashill et al., 2013), health related quality of life (EQ-5D)(Johnson and Coons, 1998; Johnson et al., 1998; Miners et al., 2014; Wu et al., 2002), depression symptoms (Patient Health Questionaire-9, PHQ-9)(Kroenke et al., 2001), and other domains. Of note, use of e-cigarettes/vaping was not common when the assessment was initially developed but was added during the study period and therefore is only available from 58% of PWH. Institutional approval to participate in CNICS was granted at each site.

2.4 Frailty

We defined frailty using a modified definition of the Fried frailty phenotype based on 4 of the 5 components(Fried et al., 2001): exhaustion/severe fatigue, unintentional weight loss/wasting, low mobility, and low physical activity. We did not capture the 5th Fried frailty phenotype component - muscle weakness. This approach is similar to what has been previously used and validated definitions of an adapted Fried frailty phenotype using self-reported approaches and/or only four of the components(Akgun et al., 2014; Sung et al., 2020). Fatigue and weight loss were obtained from the HIV Symptom Index: PWH were asked whether they had experienced symptoms of fatigue/loss of energy and weight loss/wasting over the prior 4 weeks on a 5-point Likert-type scale ranging from 0, "I do not have this symptom," to 4, "I have this symptom and it bothers me a lot." Low mobility was obtained from an EQ-5D index item with responses about current mobility on a 3-point scale ranging from "I have no problems walking about" to "I am unable to walk." Low physical activity was obtained from the LRCQ physical activity item asking PWH if they engage in strenuous exercise compared to others of their age and sex. PWH responded on a five-point scale from 1, "much less," to 5, "much more." Results for all frailty components were dichotomized (Appendix Table 1). PWH were categorized as not frail if they reported 0 components, prefrail if they reported 1-2 components, and frail if they reported 3 or 4 components of fatigue, weight loss/wasting, low mobility, and low physical activity(Desquilbet et al., 2007).

2.5 Drug and Alcohol Use

There are several ways to score the ASSIST drug use measure(Newcombe et al., 2005; 2002). We categorized use of 4 groups of drugs (marijuana, cocaine/crack, methamphetamines/crystal, and illicit opioids/heroin) as current (past 3 months), former, or never(Crane et al., 2021). Cigarette use and e-cigarette use/vaping were also categorized as current, former, or never use. We used AUDIT-C scores to categorize alcohol use over the prior year into no current alcohol use (AUDIT-C score of 0) with a prior alcohol use disorder (AUD) or without a prior AUD, non-hazardous alcohol use (AUDIT-C scores of 1-4 for men, 1-3 for women), and hazardous alcohol use (AUDIT-C score of ≥5 for men and ≥4 for women)(Bush et al., 1998; Gual et al., 2002). We used two previously successful strategies(Bradley et al., 2004) to identify probable prior AUD among current non-drinkers: 1) diagnosed with an AUD in the electronic health record, and 2) self-reported on the clinical assessment attending alcohol treatment or Alcoholics Anonymous.

2.6 Statistical Analyses

We performed bivariate analyses using chi-squared tests and *t*-tests. We compared demographic and clinical information from PWH who completed the clinical assessment and were therefore included in the study to those who did not complete an assessment during the study period. We examined the prevalence of frailty and prefrailty by demographic (i.e., age, race/ethnicity, sex, HIV transmission risk factor) and clinical characteristics including current and nadir/lowest $CD4^+$ cell counts (≤350, 350-499, and ≥500 cells/mm^3). We examined frailty and prefrailty prevalence among PWH who reported current and former drug use overall and by type of drug.

We used ordinal logistic regression for adjusted analyses comparing PWH by frailty status (not frail, prefrail and frail). Ordinal logistic regression makes assumptions about similarities of associations with each outcome, and these models failed this assumption of proportional odds (Appendix Table 2). We therefore repeated analyses using multivariate Poisson regression with 3 models to examine factors associated with prefrail vs. not frail; frail vs. prefrail; and frail vs. not frail. Models included demographic characteristics and drug use, alcohol use, and cigarette smoking.

Sensitivity analyses included repeating models stratified by sex to examine findings separately for women and men. These stratified models included similar covariates as main models apart from excluding sex and HIV transmission risk factor of men who have sex with men. We performed sensitivity analyses that included current CD4 count categories and that included viral load suppression (<200 copies/mL). We conducted sensitivity analyses using a more conservative definition of pre-frail categorizing PWH as not frail if they reported 0-1 components, prefrail if they reported 2 components, and frail if they reported 3-4 components. Among the subset (58%) who completed the assessment after the addition of the e-cigarette measure, we conducted sensitivity analyses including e-cigarette use. Due to substantial overlap in patterns of use across drug categories, we also examined associations with frailty in adjusted analyses examining each drug category in separate models. Each of these models adjusted for age, sex, race/ethnicity, alcohol and tobacco cigarette use, and one type of drug. We examined cigarette and alcohol use in a single model without any other drug use categories. Due to associations between alcohol use and other substances including cigarette use, we also conducted sensitivity analyses examining alcohol use in limited models without smoking or drug use. All analyses were performed using Stata 16 (College Station, TX:StataCorp LLC).

3. Results

3.1 Descriptive characteristics of PWH overall, and by frailty status

Between 2016-2019, the clinical assessment was completed by 9,336 PWH as part of clinical care at 7 CNICS sites across the U.S. Mean age was 49 (SD 12) years with 4,967 (53%) aged ≥50 and 1,666 (18%) aged ≥60, 1,393 (15%) were female, mean current CD4 count was 660 cells/mm^3 (SD 336) and 8,942 (96%) were receiving ART (Table 1). Demographic and clinical characteristics of PWH who completed the clinical assessment were similar to all individuals receiving care during the study period (data not shown).

Among all 9,336 PWH, 43% were classified as not frail (0 components), 44% prefrail (1-2 components), and 13% frail (≥3 frailty components) (Table 1). Being prefrail or frail were more common among women, older PWH, and those reporting injection drug use as their HIV transmission risk factor. Being frail was more common among PWH with current CD4 <350 cells/mm^3 (Table 1).

Being frail was more prevalent among PWH who reported current drug use (15%) compared with former (13%) or never using drugs (9%) (Table 2). This pattern was consistent across most drugs. For example, the prevalence of being frail among those with current illicit opioid use was 22% compared with 11% among those who had never used illicit opioids.

The prevalence of being frail among those reporting current methamphetamine use was 17% compared to 11% among those who never used methamphetamines. The prevalence of being frail was higher among PWH who currently smoked cigarettes (16%) vs. former smoking (12%) or having never smoked (10%). Being frail was more prevalent among PWH who no longer drank alcohol but had a history of an AUD (18%) compared with other categories of alcohol use (11-16%) (Table 2).

3.2 Factors associated with prefrailty and frailty among PWH

In adjusted analyses being female and older age were associated with higher risks of frailty or prefrailty vs. being not frail. Female sex was associated with a 67% greater risk of being frail vs. not frail (1.67; 95% confidence interval (CI) 1.43-1.96) and a 25% greater risk of being prefrail vs. not frail (1.25; 95% CI:1.16-1.35). The risk of being frail vs. not frail was 30% higher for every decade of older age (1.30; 95%CI:1.25-1.36) (Table 3).

Current methamphetamine use and illicit opioid use were associated with greater risk of being prefrail vs. not frail; frail vs. prefrail; and frail vs. not frail in adjusted analyses (Table 3). For example, current methamphetamine use was associated with a 26% higher risk of being frail vs. not frail (1.26; 95%CI:1.07-1.48) and current illicit opioid use was associated with a 65% higher risk of being frail vs. not frail (1.65; 95%CI:1.39-1.97). In addition, former illicit opioid use was associated with significantly greater risk of being frail vs. not frail (1.21; 95%CI:1.06-1.36) as was former cocaine/crack use (1.17; 95%CI:1.01-1.35). Both former and current marijuana use were associated with a greater risk of being prefrail vs. not frail although other comparisons for marijuana use were not significant.

Current cigarette smoking was associated with greater risk of being prefrail vs. not frail; frail vs. prefrail; and frail vs. not frail (Table 3). For example, current smoking use was associated with a 61% greater risk of being frail vs. not frail (1.61; 95%CI:1.41-1.85). In addition, former smoking was associated with an 8% greater risk of being prefrail vs. not frail (1.08; 95%CI:1.02-1.15). Both current non-hazardous and hazardous alcohol use were associated with lower risks of being pre-frail and frail, compared to not frail (Table 3).

3.3 Sensitivity analyses

We conducted analyses stratified by sex (Appendix Tables 3a and 3b). Several associations among women were similar to findings in the main model but were not statistically significant, likely due to smaller sample size in stratified analyses. In addition, current cocaine/crack use was associated with greater risk of being prefrail vs. not frail and of being frail vs. not frail among women (Appendix Table 3b) and former cocaine/crack use was associated with greater risk of being frail vs. not frail among women.

In sensitivity analyses that included current CD4 count or viral load, the overall patterns of findings were similar (Appendix Tables 4, 5). In addition, having a current CD4 count <350 cells/mm^3 (1.32; 95%CI:1.17-1.48) or a current viral load >200 copies/mL (1.58; 95%CI:1.39-1.78) were associated with a greater risk of being frail vs. not frail.

In sensitivity analyses using a more conservative definition of prefrailty requiring the presence of 2 components rather than 1-2 components, current cocaine use and former

illicit opioid use were associated with a greater risk of being pre-frail vs. not frail (Table 4) however overall the pattern of findings was similar to Table 3.

We conducted sensitivity analyses that added e-cigarette use/vaping (Appendix Table 6) and found generally similar overall patterns although former cigarette smoking was not significantly associated with a greater risk of being pre-frail vs. not frail. In addition, former e-cigarette use was associated with a greater risk of being pre-frail vs. not frail and of being frail vs. not frail. Current e-cigarette use was also associated with a greater risk of being pre-frail vs. not frail.

We conducted sensitivity analyses looking at each category of drug use in distinct models that did not include other drugs as well as a model for cigarettes and alcohol use (Appendix Table 7). Current and former use of all drugs were associated with frailty vs. no frailty in these limited models. Patterns for alcohol use and cigarette use were similar to the main model in Table 3.

In sensitivity analyses of alcohol use in models that did not include other substances, (Appendix Table 8), no current alcohol use in the setting of a history of having an AUD (vs. no current alcohol use without a prior AUD) was associated with a higher risk of being prefrail vs. not frail (1.12 95% CI: 1.01-1.24).

4. Discussion

In this study of 9,336 adult PWH in routine care at 7 clinics across the United States from 2016-2019, we found a high prevalence of prefrailty (44%) and frailty (13%). The prevalence of frailty and prefrailty were higher among women and older PWH. Substance use was associated with a higher risk of frailty in adjusted analyses: specifically, a higher risk of being frail was associated with current methamphetamine and illicit opioid use as well as former illicit opioid use. Smoking cigarettes was also associated with a much higher risk of being prefrail and frail. In addition, among women, current and former cocaine/crack use were both associated with a higher risk of being frail.

4.1 Measurement

Approaches to measuring frailty vary, and best approaches for clinical settings is controversial(Cesari et al., 2014) particularly given that different instruments and approaches result in different prevalence rates(Yeoh et al., 2018). Fried and colleagues developed the most commonly used approach, the Fried frailty phenotype based on exhaustion, physical wasting, slow walking speed, low physical activity, and decreased strength(Ahmed et al., 2007; Fried et al., 2001; Fried and Mor, 1997; Walston et al., 2006). The Fried frailty phenotype has since been modified in many ways which has led to important impacts on measured frailty rates(Theou et al., 2015). Some of these changes have made it more feasible for use in clinical settings including use of self-report instruments to assess key components such as physical activity levels(Akgun et al., 2014; Desquilbet et al., 2007; Maffei et al., 2020; Onen et al., 2009; Piggott et al., 2013; Sung et al., 2020). We focused on 4 of the 5 criteria in the Fried's phenotype, an approach sometimes referred to as the frailty-related phenotype, as has been used in studies of PWH previously(Akgun et al., 2014;

Desquilbet et al., 2011; Desquilbet et al., 2007), variations of which have been associated with hospitalizations(Akgun et al., 2014), developing AIDS(Desquilbet et al., 2011), and mortality(Akgun et al., 2014; Desquilbet et al., 2011) as well as correlating highly with the traditional Fried's phenotype (r=0.83) (cit). We used a 3-level frailty outcome variable (not frail, pre-frail, and frail) as has been previously used, although in contrast to prior studies (e.g.,(Kooij et al., 2016)), we did not use ordinal logistic regression as it did not meet proportional odds assumptions.

4.2 Drugs

The association of drug use with frailty is an important and unanswered question, particularly given the high rates of drug use among PWH, the impact of substance use on premature aging or comorbidities(Bachi et al., 2017), and because it is a modifiable risk factor(Altice et al., 2011; Celentano and Lucas, 2007; Springer et al., 2010). Several prior studies were limited by only examining injection drug use rather than individual drug classes(Althoff et al., 2014), or examined smoking and alcohol use without other drugs(Beanland et al., 2020), or focused on one specific substance (e.g., methamphetamine(Paolillo et al., 2019)) without consideration of others. These are potentially problematic approaches given the high rates of overlapping drug use and drug and alcohol use(Crane et al., 2017). The ALIVE cohort of individuals with and without HIV with a history of injection drug use did not find an association between frailty and recent injection drug use, smoking, or alcohol use in adjusted models but did find an independent association between frailty risk and use of prescription drugs not as prescribed(Piggott et al., 2013). We found the prevalence of being frail was higher among current users of all drugs vs. former users, and the prevalence of frailty among former users was higher than among non-users. Furthermore, the associations with current use are arguably an underestimate as multi-morbidity including frailty may lead some to stop their drug use(Han et al., 2018). These patterns were unchanged adjusting for viral load suggesting substance use impacts were not mediated through poorer HIV control. Adjusted analyses demonstrated that current use of illicit opioids and methamphetamines were associated with a higher risk of being frail. Findings demonstrated a higher risk of being frail among women who reported current or former use of cocaine/crack.

4.3 Cigarettes and e-cigarettes/vaping

In the general population, cigarette smoking has been associated with frailty in some, but not all studies(Feng et al., 2017). Findings of associations with cigarette smoking and frailty among PWH are inconsistent, with some studies suggesting no association(Morgello et al., 2019; Onen et al., 2009; Piggott et al., 2013), or finding associations with developing frailty in univariate analyses of PWH but not in analyses adjusted for demographic and other factors(Althoff et al., 2014), or finding suggestive but not significant associations (including PWH and those without HIV)(Kooij et al., 2016). A study that combined past and current smoking together found the odds of an increase in frailty level was significantly higher (odds ratio 1.37) among PWH who smoked(Erlandson et al., 2017). Similarly, a study of women with and without HIV found past and current smoking combined was associated with frailty(Gustafson et al., 2016). Many of these prior studies have been limited by sample size. The current study builds on these findings by having the large sample size and rich smoking

measurement to allow current and former cigarette smoking to be assessed independently. In addition, it allows exploration of associations between e-cigarette use and frailty. We found former and current cigarette smoking and former e-cigarette use were associated with greater risk of being prefrail or frail, that current e-cigarette use was associated with a higher risk of being prefrail, and the greatest risk was among those who currently smoked cigarettes.

4.4 Alcohol

Alcohol use has been hypothesized to accelerate aging and frailty among the general population although studies have revealed mixed findings including protective effects and no associations(Feng et al., 2017). However, alcohol use rates among PWH are high(Crane et al., 2017), and as a potentially modifiable risk factor, a better understanding of any role of alcohol use in frailty among PWH is needed.

Among PWH to date, findings of alcohol use and frailty have been mixed with some studies demonstrating no associations(Onen et al., 2009), and others finding increased frailty risk(Piggott et al., 2020) or protective(Erlandson et al., 2017) associations particularly with light or moderate use(Erlandson et al., 2017; Gustafson et al., 2016). A concern has been raised that much of what has been studied is based on recent or current alcohol use rather than broader alcohol history, leading to the inference that alcohol protects from frailty(Maffei et al., 2020). The need for additional exploration of the relationships between frailty and alcohol use have therefore been noted(Maffei et al., 2020). One of the best studies examining associations between alcohol use and frailty among PWH was from the New Orleans Alcohol Use in HIV Study. Among 365 PWH, lifetime alcohol use was associated with frailty while current alcohol use had an inverse association with frailty(Maffei et al., 2020). A strength of the New Orleans Alcohol Use in HIV Study compared to most prior studies is it also incorporated smoking, although it used a composite variable for drug use rather than adjusting for different drugs(Maffei et al., 2020). The AGEhiV cohort found that current alcohol use was less common among frail individuals and also inversely associated with mortality(Verheij et al., 2020). This led them to hypothesize that unhealthy participants had likely reduced their consumption of or stopped drinking alcohol(Verheij et al., 2020). This hypothesis is supported by our findings of the lower risk of being frail among PWH who currently drink combined with differences in prefrailty risk among those who currently did not drink with and without a history of an AUD. By separating the current non-drinkers into those with a prior AUD and those without, we were able to build on the findings of the AGEhiV cohort and begin to tease apart the impact of prior AUD among PWH who currently do not drink.

4.5 Strengths

A strength of the study is the large, diverse cohort of PWH in the current HIV treatment era. This cohort represents the changing epidemiology of HIV across the United States with substantial numbers of women, racial and ethnic minority participants, and older PWH in clinical care. Strengths of CNICS include the comprehensive clinical data including substance use assessments. The focus on substance use including both current and former use is important given the high prevalence rates among PWH and that substance use has often not been addressed in frailty and HIV studies and in some cases even used as an

exclusion factor for study participants(Shah et al., 2012). We found similar patterns of findings using a more conservative or stringent criteria for pre-frailty. The large sample size with as many as 5-10 times more PWH than many of the studies to date(Althoff et al., 2014; Erlandson et al., 2017) is an important strength.

4.6 Limitations

The cross-sectional nature limits causal inferences regarding relationships between substance use and frailty and does not address the dynamic nature of frailty including an individual's possible progression or recovery over time(Kojima et al., 2019). There is debate regarding best criteria for defining frailty(Rodriguez-Manas et al., 2013) and because we assessed four of the five phenotypic components, we may have underestimated frailty. CNICS may not generalize to PWH who do not yet know they have HIV or are not in clinical care. In addition, while the CNICS clinical assessment has recently been expanded to include Amharic, the current study included only English and Spanish-speaking PWH at sites across the United States, which further limits generalizability. The CNICS clinical PRO assessment is, by definition, self-reported. However, electronic collection of PROs reduces patient burden, permits integration of PROs into care and decreases underreporting of risk behaviors due to social desirability bias(Fairley et al., 2010). Furthermore, it allows capture of key components of frailty such as fatigue however capture of these components is limited to the available response options. Finally, for these analyses we included assessments from 2016 or later to be relevant to PWH currently alive and in care but excluded data from 2020 and after to not allow pandemic-driven impacts on clinical care or physical activity to impact the findings.

4.7 Future studies

There are additional questions for future studies. We are particularly interested in expanding the evaluation of prior AUD in longitudinal analyses, examining the role of comorbidities, and examining the dynamic nature of frailty among PWH including the extent it is reversible or potentially modifiable. Future longitudinal studies in CNICS will also provide more information on consequences of frailty among PWH.

4.8 Conclusions

This study evaluated the prevalence and correlates of frailty in a large, diverse cohort of PWH. Frailty is common in the current HIV treatment era. This study demonstrated that multiple distinct factors may be associated with frailty, and many of which, such as smoking, are potentially addressable. Additional longitudinal studies will help clarify the potential causal role of some of these associations. Assessing frailty as part of routine HIV care could be useful for risk stratification and minimizing poor health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of interest and sources of funding:

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Data statement:

This paper used data from CNICS. Deidentified CNICS data is available to researchers with an approved concept proposal. See https://sites.uab.edu/cnics/ for more details on CNICS data sharing.

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Table 1.

Demographic and clinical characteristics by frailty status among people with HIV in clinical care at 7 sites across the United States, 2016-2019 (n=9,336)

Characteristic [a]	Overall [b] (n=9,336) 100% n (%)	Not frail [c] (n=4,033) 43% n (%)	Prefrail [c] (n=4,092) 44% n (%)	Frail [c] (n=1,211) 13% n (%)	p-value
Sex					
Female	1,393 (15)	494 (35)	660 (47)	239 (17)	<0.001
Male	7,943 (85)	3,539 (45)	3,432 (43)	972 (12)	
Age					
<30	482 (5)	249 (52)	215 (45)	18 (4)	<0.001
30-39	1,740 (19)	865 (50)	739 (42)	136 (8)	
40-49	2,147 (23)	942 (44)	937 (44)	268 (12)	
50-59	3,301 (35)	1,337 (41)	1,431 (43)	533 (16)	
≥60	1,666 (18)	640 (38)	770 (46)	256 (15)	
Race/ethnicity					
White	4,507 (48)	1,836 (41)	2,041 (45)	630 (14)	<0.001
Black	2,860 (31)	1,306 (46)	1,229 (43)	325 (11)	
Hispanic	1,458 (16)	669 (46)	603 (41)	186 (13)	
Other	511 (5)	222 (43)	219 (43)	70 (14)	
HIV transmission risk factor					
MSM	5,973 (64)	2,718 (45)	2,551 (43)	704 (12)	<0.001
Heterosexual	2,005 (21)	862 (43)	865 (43)	278 (14)	
IDU	1,074 (12)	345 (32)	533 (50)	196 (18)	
Other	284 (3)	108 (38)	143 (50)	33 (12)	
Nadir (lowest) CD4 count (cells/mm^3)					
<350	6,143 (66)	2,633 (43)	2,686 (44)	824 (13)	0.24
350-499	1,509 (16)	681 (45)	644 (43)	184 (12)	
≥500	1,684 (18)	719 (43)	762 (45)	203 (12)	
Current CD4 count (cells/mm^3)					
<350	1,586 (17)	598 (38)	713 (45)	275 (17)	<0.001
350-499	1,532 (16)	641 (42)	685 (45)	206 (13)	
≥500	6,218 (67)	2,794 (45)	2,694 (43)	730 (12)	
Receiving ART	8,942 (96)	3,883 (43)	3,902 (44)	1,157 (13)	0.11
HIV viral load (copies/mL)					
Detectable (≥200)	889 (10)	301 (34)	406 (46)	182 (20)	<0.001
Undetectable (<200)	8,435 (90)	3,728 (44)	3,681 (44)	1,026 (12)	

ART: antiretroviral therapy; BMI: body mass index; MSM: men who have sex with men; IDU: injection drug use

Not frail: 0 symptoms; Prefrail: 1-2 symptoms; Frail: 3-4 symptoms

[a] Data presented as n (%)

[b] Column percentage

[c] Row percentage

Table 2.

Substance use by frailty status among people with HIV in clinical care at 7 CNICS sites across the United States 2016-2019 (n=9,336)

Substance use [a]	Overall [b] (n=9,336) 100% n (%)	Not frail [c] (n=4,033) 43% n (%)	Prefrail [c] (n=4,092) 44% n (%)	Frail [c] (n=1,211) 13% n (%)	p-value
Any drug use					<0.001
Never	1,998 (21)	1,053 (53)	764 (38)	181 (9)	
Former	2,700 (29)	1,145 (42)	1,205 (45)	350 (13)	
Current	4,638 (50)	1,835 (40)	2,123 (46)	680 (15)	
Any drug use (excluding marijuana)					<0.001
Never	3,826 (41)	1,947 (51)	1,535 (40)	344 (9)	
Former	3,321 (36)	1,305 (39)	1,509 (45)	507 (15)	
Current	2,189 (23)	781 (36)	1,048 (48)	360 (16)	
Methamphetamine use					<0.001
Never	5,477 (59)	2,594 (47)	2,295 (42)	588 (11)	
Former	2,412 (26)	930 (39)	1,111 (46)	371 (15)	
Current	1,447 (15)	509 (35)	686 (47)	252 (17)	
Cocaine/crack use					<0.001
Never	4,574 (49)	2,220 (49)	1,883 (41)	471 (10)	
Former	3,766 (40)	1,444 (38)	1,729 (46)	593 (16)	
Current	996 (11)	369 (37)	480 (48)	147 (15)	
Marijuana use					<0.001
Never	2,396 (26)	1,196 (50)	941 (39)	259 (11)	
Former	2,978 (32)	1,231 (41)	1,357 (46)	390 (13)	
Current	3,962 (42)	1,606 (41)	1,794 (45)	562 (14)	
Illicit Opioid use					<0.001
Never	6,763 (73)	3,127 (46)	2,877 (43)	759 (11)	
Former	2,088 (22)	772 (37)	970 (46)	346 (17)	
Current	485 (5)	134 (28)	245 (50)	106 (22)	
Cigarette use					<0.001
Never	3,240 (35)	1,633 (50)	1,291 (40)	316 (10)	
Former	2,560 (27)	1,110 (43)	1,134 (44)	316 (12)	
Current	3,536 (38)	1,290 (37)	1,667 (47)	579 (16)	
E-Cigarette use *					<0.001
Never	4,382 (80)	2,102 (48)	1,806 (41)	474 (11)	
Former	785 (14)	313 (40)	355 (45)	117 (15)	
Current	290 (5)	105 (36)	149 (51)	36 (12)	
Alcohol use					<0.001
No current use	1,876 (20)	728 (39)	848 (45)	300 (16)	

Substance use [a]	Overall [b] (n=9,336) 100% n (%)	Not frail [c] (n=4,033) 43% n (%)	Prefrail [c] (n=4,092) 44% n (%)	Frail [c] (n=1,211) 13% n (%)	p-value
No current use, prior AUD	400 (4)	130 (33)	199 (50)	71 (18)	
Non-hazardous	4,643 (50)	2,082 (45)	1,993 (43)	568 (12)	
Hazardous	2,417 (26)	1,093 (45)	1,052 (44)	272 (11)	

Not frail: 0 components; Prefrail: 1-2 components; Frail: 3-4 components

AUD: Alcohol use disorder

[a] Data presented as n (%)

[b] Column percentage

[c] Row percentage

[*] E-cigarette use based on 58% of study participants as introduced to the clinical assessment partway through the study period

Table 3.

Factors associated with frailty status among people with HIV in clinical care at 7 sites across the US in 2016-2019 in adjusted analyses by frailty category

	Prefrail vs. Not frail				Frail vs. Prefrail				Frail vs. Not frail			
	RR	[95% Conf. Interval]		p-val	RR	[95% Conf. Interval]		p-val	RR	[95% Conf. Interval]		p-val
Female	1.25	1.16	1.35	<0.001	1.31	1.11	1.56	0.002	1.67	1.43	1.96	<0.001
Age (per decade)	1.05	1.03	1.07	<0.001	1.21	1.16	1.27	<0.001	1.30	1.25	1.36	<0.001
Race/ethnicity												
White (ref)												
Black	0.96	0.91	1.01	0.13	0.94	0.82	1.07	0.33	0.91	0.80	1.03	0.13
Hispanic	0.96	0.90	1.02	0.21	1.13	0.98	1.30	0.11	1.03	0.89	1.18	0.73
Other	0.99	0.90	1.10	0.91	1.13	0.92	1.40	0.25	1.11	0.90	1.36	0.34
MSM	1.02	0.95	1.09	0.57	1.01	0.87	1.18	0.88	1.00	0.87	1.16	0.95
Methamphetamine												
Never (ref)												
Former	1.03	0.97	1.10	0.30	1.10	0.95	1.28	0.21	1.12	0.97	1.30	0.13
Current	1.08	1.00	1.16	0.04	1.21	1.03	1.43	0.02	1.26	1.07	1.48	0.005
Cocaine/crack												
Never (ref)												
Former	1.04	0.97	1.10	0.26	1.09	0.95	1.26	0.22	1.17	1.01	1.35	0.04
Current	1.08	0.99	1.17	0.07	0.97	0.80	1.18	0.80	1.13	0.93	1.36	0.21
Marijuana												
Never (ref)												
Former	1.09	1.02	1.17	0.01	0.88	0.75	1.04	0.13	1.01	0.86	1.19	0.88
Current	1.11	1.03	1.19	0.005	0.98	0.83	1.16	0.82	1.16	0.98	1.37	0.09
Illicit Opioid												
Never (ref)												
Former	1.05	0.99	1.11	0.11	1.10	0.97	1.25	0.12	1.21	1.06	1.36	0.003
Current	1.18	1.08	1.29	<0.001	1.29	1.07	1.56	0.009	1.65	1.39	1.97	<0.001
Cigarette												
Never (ref)												
Former	1.08	1.02	1.15	0.01	1.04	0.90	1.20	0.59	1.16	1.00	1.34	0.053
Current	1.18	1.12	1.25	<0.001	1.26	1.10	1.44	0.001	1.61	1.41	1.85	<0.001
Alcohol												
Non-drinker (ref)												
Non-drinker, prior AUD	1.04	0.94	1.15	0.47	0.97	0.77	1.22	0.79	1.02	0.83	1.26	0.85
Non-hazardous	0.91	0.86	0.96	0.001	0.90	0.79	1.02	0.09	0.78	0.69	0.88	<0.001
Hazardous	0.87	0.81	0.93	<0.001	0.80	0.69	0.93	0.004	0.65	0.56	0.75	<0.001

In addition to above variables, also adjusted for PRO year

AUD: Alcohol use disorder; MSM: men who have sex with men

Not frail: 0 components; Prefrail: 1-2 components; Frail: 3-4 components

Table 4.

Factors associated with frailty status among people with HIV in clinical care at 7 sites across the US in 2016-2019 in adjusted analyses by frailty category using a frailty definition with a more conservative definition of prefrailty*

	Prefrail vs. Not frail				Frail vs. Prefrail				Frail vs. Not frail			
	RR	[95% Conf. Interval]		p-val	RR	[95% Conf. Interval]		p-val	RR	[95% Conf. Interval]		p-val
Female	1.39	1.19	1.62	<0.001	1.15	0.99	1.33	0.07	1.64	1.38	1.94	<0.001
Age (per decade)	1.14	1.09	1.18	<0.001	1.11	1.06	1.15	<0.001	1.32	1.26	1.38	<0.001
Race/ethnicity												
White (ref)												
Black	0.92	0.82	1.03	0.17	0.99	0.89	1.11	0.87	0.89	0.78	1.02	0.11
Hispanic	0.99	0.86	1.13	0.87	1.07	0.94	1.21	0.30	1.09	0.94	1.27	0.27
Other	0.94	0.76	1.16	0.57	1.14	0.96	1.37	0.14	1.11	0.89	1.38	0.37
MSM	0.96	0.84	1.09	0.50	1.04	0.91	1.18	0.57	0.99	0.85	1.15	0.90
Methamphetamine												
Never (ref)												
Former	0.99	0.87	1.14	0.91	1.09	0.97	1.24	0.15	1.11	0.94	1.30	0.22
Current	1.04	0.89	1.21	0.60	1.16	1.01	1.33	0.03	1.27	1.06	1.51	0.008
Cocaine/crack												
Never (ref)												
Former	1.08	0.94	1.23	0.28	1.05	0.93	1.18	0.44	1.17	1.00	1.36	0.054
Current	1.23	1.04	1.46	0.02	0.91	0.77	1.08	0.29	1.11	0.90	1.36	0.32
Marijuana												
Never (ref)												
Former	1.15	0.99	1.33	0.07	0.89	0.77	1.02	0.09	0.97	0.81	1.15	0.71
Current	1.20	1.03	1.40	0.02	0.94	0.82	1.09	0.42	1.12	0.94	1.34	0.21
Illicit Opioid												
Never (ref)												
Former	1.20	1.07	1.35	0.001	1.00	0.90	1.12	0.94	1.23	1.08	1.40	0.002
Current	1.41	1.17	1.69	<0.001	1.11	0.94	1.31	0.21	1.61	1.33	1.96	<0.001
Cigarette												
Never (ref)												
Former	1.12	0.98	1.27	0.09	1.00	0.89	1.14	0.95	1.14	0.97	1.32	0.11
Current	1.36	1.20	1.53	<0.001	1.09	0.98	1.23	0.12	1.56	1.35	1.80	<0.001
Alcohol												
Non-drinker (ref)												
Non-drinker, prior AUD	0.98	0.79	1.21	0.85	1.02	0.84	1.23	0.85	0.95	0.75	1.20	0.65
Non-hazardous	0.85	0.75	0.95	0.005	0.96	0.87	1.07	0.50	0.78	0.69	0.89	<0.001
Hazardous	0.77	0.67	0.89	<0.001	0.91	0.80	1.03	0.14	0.66	0.56	0.77	<0.001

In addition to above variables, also adjusted for PRO year

AUD: Alcohol use disorder; MSM: men who have sex with men

Not frail: 0-1 components; Prefrail: 2 components; Frail: 3-4 components