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Annals of Immunology & Immunotherapy
ISSN: 2691-5782

Frailty and Comorbidities in Adult People Living with HIV a Case Study in Uzumba Maramba Pfungwe District, Mashonaland East Province, Zimbabwe

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Short Communication
Volume 4 Issue 1
Received Date: January 17, 2022
Published Date: February 23, 2022
DOI: 10.23880/aii-16000162

Abstract

Some evidence suggests that HIV itself is associated with frailty; a syndrome typically viewed as being related to ageing. The researcher determines the prevalence and predictors of frailty in a population of HIV infected individuals at Mutawatawa Hospital in UMP district, Mashonaland East, Zimbabwe. He also determined the association between frailty and comorbidities. A retrospective cohort study of 153 adults (>30 years) people living with HIV was used. The mean age of the study participants was 44.49 and a median of 41. The majority were female (62.7%). Frailty as defined by standardized assessment comprised of ≥3 of weight loss, low physical activity, exhaustion, weak grip strength and slow waling time. 64.7% of the study participants were found to be frail. Independent predictors of frailty were evaluated using Binary logistic regression. Association between frailty and comorbidities was determined using Binary logistic regression. CD4 count was a strong predictor of frailty (OR=1.33; 95% CI: 1.03-5.74, p=0.026). Age was also a strong predictor of frailty (OR=2.993; 95% CI: 1.049-3.039, p=0.023). Type-2 Diabetes Mellitus (OR=3.59; 95% CI: 1.028-4.53; p=0.029), CVD (OR= 1.632; 95% CI: 1.117-22.735; p=0.015) and dyslipidemia (OR=0.713; 95% CI: 1.020-25.275; p=0.042) were strongly associated with frailty. Lower CD4 counts and older age were strong predictors of frailty in HIV infected populations. Earlier initiation of ART may be protective. Type-2 Diabetes Mellitus, CVD and Dyslipidemia were strongly associated with frailty. A cardiovascular exercise regimen can help overcome frailty.

Keywords: HIV; Antiretroviral Therapy; Opportunistic Infections; Type-2 Diabetes Mellitus

Abbreviations: HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy

Introduction

Owing to the success of antiretroviral therapy (ART) in increasing the lifespan of people living with HIV (PLHIV) and the incidence of HIV infection. PLHIV population has been increasingly ageing with median age around 50 years in most Western clinics [1]. As a result, frailty has rapidly become a problem to HIV patients. Increasing evidence suggests that while PLHIV does not age prematurely, concerns about the frailty commonly seen in the geriatric population can often be seen in HIV patients 10 years or older. In addition, the

prevalence of comorbidity, multi-morbidity, and frailty in PLHIV is higher than in the general population at all ages and the difference between the two populations widens with age [2]. Several factors predispose PLHIV to higher rates of frailty, including the effects of chronic HIV inflammation (even with complete plasma virological suppression), toxic effects of earlier antiretroviral regimens, delayed initiation of HIV therapy, higher rates of multi-morbidity (presence of two or more chronic medical conditions) and co-infection, HIV-associated neurocognitive, disorder, lifestyle factors such as smoking, poverty and social isolation [3].

Background

Large decreases in HIV-associated mortality have occurred because of the increased use of ART globally. There is evidence that patients receiving ART are at an elevated risk of age-related non-AIDS morbidity and mortality relative to HIV-negative individuals. Several of these conditions are commonly associated with the natural aging cycle but tend to occur at an earlier age in HIV-infected individuals relative to age-matched HIV-negative individuals [4]. HIV cohorts may not only age chronologically but may also experience rapid physiological and immunological senescence. Frailty is a psychiatric condition that was initially identified in geriatric populations. It represents the idea of a diminished physiological and functional reserve and a consequent decline in tolerance to external or intestinal stressors. Frailty is characterized by multiple pathologies, poor physical activity, and sluggish motor performance, which leads to cognitive and physical impairment manifested as an increased risk of mortality, falls and hospitalization. HIV infection has been associated with premature development of frailty and has been suspected to be a significant clinical condition in HIV-infected persons [5]. The epidemiology of HIV and AIDS in sub-Saharan Africa (SSA) is changing; a wide scale of ART has contributed to decreased death rates and a steadily growing population of HIV-infected African patients living much longer than ever [6].

Nevertheless, it is not known if these individuals will also be susceptible to premature aging in the longer term. Estimates from prior research in Europe and North America, where HIV epidemiology varies significantly from that in sub-Saharan Africa, may not be generalizable to African HIV cohorts. Zimbabwe's disease climate, like most SSA nations, has until recently been dominated by HIV / AIDS. However, there is increasing awareness of the contribution of NCDs to the burden of morbidity and mortality in the general population. So far as the HIV infected population is concerned, the effect of comorbid NCDs and the effects they have on the individual's physiological and functional reserve remain uncertain. This is given the fact that HIV prevalence currently stands at 15% of the 14 million population (Zimbabwe National HIV and AIDS Estimates Survey, 2015 [7]. As a result, the evidence base for objectively informing approaches and methods to effectively tackle these current and rapidly rising problems in SSA is weak. Knowing the burden of NCD for those living and aging with HIV is important if the advances already achieved in the fight against HIV are to be sustained. As an initial step in mapping the NCD-HIV comorbidity and frailty terrain in low income, high HIV burden settings, the study sought to describe the relationship between non-communicable disease and frailty among adults living with HIV infection in Zimbabwe. The aim of the research is to determine the predictors of frailty and assessing the association between frailty and comorbidities in HIV-infected patients in Uzumba Maramba Pfungwe district.

Research Design

A retrospective cohort study was done on HIV patients in Uzumba Maramba Pfungwe. A retrospective cohort design was more appropriate for this study because a prospective study takes time before an event of interest takes place. Additionally, the data for the patients was already collected in the HIV registers making it convenient to use the retrospective cohort design. This study involved a historical analysis of the adult HIV positive, from the period 1 January 2015 to 31 December 2019. The study utilized routine data in HIV patients' records to evaluate the outcomes of interest which is frailty and comorbidities. The retrospective nature of the study disclosed the effect of the risk factors identified, and the extent at which they influenced frailty and comorbidity.

Sampling Procedures

Kumar [8], defines a sample as a subgroup of the population which is the focus of the research enquiry. Defining the target population helps the researcher to appreciate the most appropriate methodology to use for sampling. A proper definition or specification of the population is critical because it guides others in appraising the credibility of the sample, sampling technique(s) and outcomes of the research [9]. A sampling frame is a list or device used to define the researcher's population of interest. In this study the sampling frame was the admission register for HIV patients. The third step is choosing a sampling technique, and two major techniques identified are the probability and non-probability sampling techniques. Probability sampling techniques are ideal for quantitative studies. The fourth and critical step in the sampling process is determining the sample size. Emphasize that three or four factors must be known or estimated to calculate sample size: the effect size

(usually the difference between 2 groups); the population standard deviation (for continuous data); the desired power of the experiment to detect the postulated effect; and the significance level.

Kadam and Bhalerao [10], confirm that the sample size for any study depends on the acceptable level of significance, Power of the study, expected effect size, underlying event rate in the population and the standard deviation in the population. However, all 153 HIV patients who were receiving ART at Mutawatawa hospital were included in this study. A total of 153 participants were used because they had their information available in the HIV registers.

Target Population

Unselected HIV-infected individuals of more than 30 years of age were enrolled from a community-based HIV treatment Centre in UMP district of Mashonaland East province. All participants should have a confirmed serological diagnosis of HIV and are either about to commence ART (ART-naïve), or are already on first-line ART. Participants with active opportunistic infections (OIs) were not recruited; however participants with active TB (i.e. non-symptomatic but still receiving treatment for TB) were enrolled.

Assessment of Frailty and data Collection

Physical frailty was defined by the presence of ≥3 of 5 criteria: i) unintentional weight loss, ii) self-reported low physical activity, iii) self-reported exhaustion, iv) weak grip strength and v) slow walking time. All these five components described in the original phenotype by Fried et al. were used to determine the presence of frailty. Socio-demographic information and medical history were obtained via a questionnaire administered in the participants. HIV-related conditions were classified according to the WHO staging system and be based upon historical assessment done at the time of enrolment into the ART service. ART was defined as the use of ≥3 antiretroviral drugs, and treatment duration was recorded in months. CD4 count and HIV RNA plasma viral load (VL) were available from medical records and HIV registers obtained from HIV treatment center, Mutawatawa General Hospital. Viral load suppression was defined as HIV RNA <50 copies/mL. This study mostly used data obtained from medical and demographical records.

Variables of Interest in the Study

The response variable in this research is the "frailty. The predictor variables of interest include some demographic variables of the subjects and medical related variables, which in one way or the other affect the association between frailty and comorbidity. The predictor variables include the following classifications; Age in years (30-39, 40-49, 50-59 and >60years), Gender, Marital status, CD4 count, Employment status, Education, Antiretroviral therapy, Comorbid disorders (Diabetes mellitus only/Hypertension only/Both Diabetes mellitus and hypertension/CVD, Dyslipidemia Others).

Ethical Consideration

The researcher sought ethical approval from the Medical Superintendent of UMP District hospital. Information gathered from hospital records was used for the purpose of this study. The researcher did not publish any name from the registers. Written informed consent was obtained in accordance with the Helsinki Declaration and the researcher used hospital records. As this study involves secondary data, waiver for informed consent was sought.

Data Analysis

Analysis was conducted on participants with criteria available for determination of frailty phenotype (3 or more of the criteria present). Participants were categorized as 'frail' and 'non-frail'. Univariable logistic regression was performed to select factors associated with frailty. HIV-infected individuals were also analyzed based upon their ART status (naive or on treatment). Descriptive analysis was contacted using SPSS software. A p-value < 0.05 was considered statistically significant as shown in the results section. The Chi-Square test was used to test for association between frailty and comorbidities. Binary logistic regression was used to predict the relationship between predictors (independent variables) and the response variable (predicted variable) where the response variable was binary

Results

Demographic Characteristics

Majority of the patients were in the 30-39 age groups whilst a small proportion was over 60 years. The cohort had more females than males. The majority (53.6%) of the patients were married, with the rest assuming other marital statuses categorised as single, divorced, or widowed. The larger proportion of the population is unemployed and stays in the rural area in UMP district. See Tables 1-3 for details.

Variable		Frequency	Proportion (%)
Sex	Female	96	62.7
	Male	57	37.3
	Total	153	100
Age group	30-39	65	42.5
	40-49	43	28.1
	50-59	26	17
	60+	19	12.4
	Total	153	100
Comorbid conditions	0	22	14.4
	1	70	45.6
	2	61	39.9
	Total	153	100
Employment status	Unemployed	88	57.5
	Employed	65	42.5
	Total	153	100
Smoking	Nil	119	77.8
	>5yaers	1	0.7
	5-15years	7	4.6
	15+years	25	17
	Total	153	100
CD4	Nil	40	26.1
	< 350	34	22.2
	350 - 500	33	21.6
	> 500	46	30.1
	Total	153	100
Alcohol per week	Nil	104	68
	<1litre	49	32
	Total	153	100
WHO stage	One	3	2
	Two	39	25.5
	Three or Four	111	72.5
	Total	153	100
ARV status	No ARV	1	0.7
	Continue ARV	146	95.4
	Change ARV	6	3.9
	Total	153	100
Education level	Primary	9	6.2
	Secondary	82	56.2
	Tertiary	55	37.7
	Total	146	100

Marital status	Single	21	13.7
	Married	82	53.6
	Widowed	36	23.5
	Divorced	8	5.5
	Missing	6	3.9
	Total	153	100

Table 1: Demographic characteristics of study population.

Condition 1	Frequency	Proportion (%)	Condition 2	Frequency	Proportion (%)
Type 2 Diabetes	19	12.4	Type 2 Diabetes	8	5.2
CVD	19	12.4	CVD	6	3.9
Obesity	17	11.1	Obesity	7	4.6
TB Previous	8	5.2	TB Previous	3	2
TB Current	9	5.9	TB current	0	0
Hypertension	25	16.3	Hypertension	16	10.5
Renal	7	4.6	Renal	9	5.6
Cancer	7	4.6	Cancer	1	0.7
Dyslipidemia	5	3.3	Dyslipidemia	2	1.3
Eating Orders	4	2.6	Eating Orders	1	0.7
Weight Loss	23	15	Weight Loss	33	21.7
Nil	10	6.5	Nil	67	43.8
Total	153	100	Total	153	100

Table 2: Summary for comorbid conditions. Adapted from Freid et al. and Onnen et al. [11].

Criteria	Definition			
Unintentional weight loss	>10 pounds weight loss documented in last year or ≥5% of previous year's body weight			
Low physical activity	Participants answering 3 when asked whether their health limits vigorous activities such as running, lifting heavy objects 1= not at all, 2= yes, limited a little, 3= yes, limited a lot			
Exhaustion	Participants answering 2 or 3 of either one of two statements- "How often have you felt that",			
	a) Everything I did was an effort or			
	b)I could not get going			
	0= rarely (<1 day), 1= some of the time (1-2 days), 2= occasionally (3-4 days) 0r 3= most of the time (5-7 days0.			
Weak grip strength	Male BMI kg/m2	kg	Female BMI kg/m2	Kg
	≤24	≤29	≤23	≤17
	24.1-26.0	≤30	23.1-26.0	≤17.3
	26.1-28.0	≤30	26.1-29.0	≤18
	>28	≤32	>29.0	≤21
Slow walking time	Male height (cm)	seconds	Female height (cm)	seconds
	≤173	≤7	≤159	≤7
	>173	≤6	>159	≤6

Table 3: Frailty criteria and definitions.

Prevalence of Frailty

Assessment of frailty was possible in all participants (n=153) with 3 excluded from walking test but still contributing to frailty data. Frailty outcomes with the study participants are reported in Table 4. The prevalence of frailty was greater among HIV patients of 30-39 age groups. Levels of pre-frail and robust (i.e scoring 0 for robust, 1and 2 for pre-frail of the frailty criteria) are more in females than in males. Of the criteria indicators, weight loss and slow walking time were common in males than in females (36.85% vs. 31.25% and 24.56% vs 21.89%). Overall, 64.7% of the study population was frail as shown in the summary table of frailty (Table 5).

Contribution	Male		Female	
	Frequency	Proportion (%)	Frequency	Proportion (%)
Weight loss	21	36.85	30	31.3
Slow walking time	14	24.56	21	21.9
Exhaustion	8	14.03	13	13.5
Weak grip strength	4	7	18	18.8
Low physical activity	7	12.28	10	10.4
None	3	5.3	4	4.2
Total	57	100	96	100

Table 4: Frequency of frailty criteria stratified by gender.

Result	Frequency	Proportion (%)
Robust	7	4.6
Pre-frail	47	30.7
Frail	99	64.7
Total	153	100

Table 5 Frequency of overall frailty status.

Predicators of Frailty

CD4 count was found to be strongly significant with a p-value of 0.026, 95% CI: 1.03-5.74 and age was also found to be significant with p-value of 0.023, 95% CI: 1.149-3.039. All the other variables are not significant (Table 6).

Variable		Coefficient	S.E.	p-value	Odds Ratio	95% C.I.	
						Lower	Upper
Step 1	CD4	0.003	0.001	0.026	1.33	1.03	5.74
	Age	-0.007	0.123	0.023	2.993	1.149	3.039
	Constant	-20.842	40192.99	1	0		

Table 6: Binary logistic regression to show association of comorbid conditions and frailty.

We also fit the logistic regression model to assess the association between comorbid conditions and frailty. Type-2 Diabetes Mellitus was found to have a strong association with frailty (p-value = 0.029). CVD was also found to be associated with frailty (p-value=0.015). Of all the comorbid conditions, CVD is 1.63 times more likely to impact frailty in HIV infected patients and the odds could be as small as 1.23 and as big as 2.16. The results showed that if Dyslipidemia was a second comorbid condition, then it can have an association with frailty (p-value=0.042) although the odds (=0.713) are showing that Dyslipidemia is protective (Table 7).

Variable	Coefficient	S.E.	p-value	Odds Ratio	95% C.I.	
					Lower	Upper
DM	-1.024	0.294	0.029	3.59	2.028	6.536
CVD	0.49	0.144	0.015	1.632	1.23	2.16
TB previous	-2.526	2.371	0.287	0.08	0.001	8.329
TB current	-3.851	1.872	0.04	0.021	0.001	0.833
Dyslipidemia	-0.339	1.821	0.042	0.713	1.02	25.275
Constant	4.553	2.047	0.026	94.946		

Table 7: Binary logistic regression to identify predictors of frailty.

Discussion

Prevalence of frailty was found to be 64.7% in this study. In other studies, carried in the United States, a prevalence of 49.3% was reported from a clinic population (mean age 42 years) [3]. The Women's Interagency HIV study (a prospective cohort in five US cities) found a prevalence of 51% in HIV infected women with clinical AIDS (median 41years). In the Multicenter AIDS cohort study (a longitudinal study of men who have sex with men), a frailty prevalence of 5-14% depending on age and duration of HIV infection was reported from 1994-2005 data and 8% in 2009-2010 among men aged 40-49 years. The variation in estimates is likely to be attributed to differences in study designs and clinical demographics. The research findings provide clear evidence that in HIV infected population, CD4 count and patient age are strongly associated with a two-fold risk of frailty. Frailty was most prevalent in women who comprise most of the study participants. The findings have potentially important implications for long-term morbidity among the millions of patients receiving ART. Age was important in measuring frailty of patients with low CD4 count.

Frailty is likely more causally related to the inflammatory state and profound immunosuppression found in many patients with low CD4 count. Many of these patients had a history of recently treated opportunistic infections. Because of this observation, I propose an active diagnosis of AIDS (CD4 count <350cells/uL) is a significant comorbidity itself and significantly predisposing patients to being frail. All the frail patients had at least one comorbidity besides HIV itself. Those patients <40 years had significantly fewer comorbidities than frail patients >40 years, though in comparison, the younger patients had a lower CD4 count. But it could be that frailty in younger patients with lower CD4 count may revert when CD4 count improve. In agreement with other studies of participants on ART, CD4 count and age were strong predictors of frailty in HIV infected individuals. In Spain, the Diabetes report found that at least 30 per cent of people between 61 and 75 years of age and over 35 per cent of people > 76 years of age have diabetes [6]. The prevalence of diabetes increases with the existence of frailty. The Cardiovascular Health Survey found that the incidence of diabetes was 18.8 per cent in non-frailty individuals, 24.5 per cent in pre-frailty individuals, and 32.4 per cent in patients with frailty. Similarly, the occurrence of frailty is higher in patients with diabetes.

Evidence from a variety of studies reviewed by other authors indicates a close association between diabetes, insulin resistance, chronic low-grade inflammation characteristic of diabetes and muscle deterioration. Many studies have shown that muscle strength and efficiency decline in patients with diabetes, and this decline becomes more pronounced the longer the patient is affected with diabetes and poorer their glycemic control. Insulin resistance is associated with decreased muscle strength, most likely due to reduced protein synthesis, increased degradation, and subsequent loss of muscle mass [4]. At the same time, insulin resistance in aging patients that lead to mitochondrial alterations that result in a decrease in the energy generation needed for muscle contraction and an increase in oxidative stress [12]. Insulin-like growth factor type 1 plays an important role in protein synthesis, and the amount of this molecule decreases with age and in patients with diabetes. Relationship was stronger in older patients than in younger patients. Newman, et al. 2013, [13] reported that CVD was associated with frailty (p=0.024, 95% CI 1.24-12.60. Art increase comorbidity risk because of altered metabolism. As HIV is associated with changes in lipids level, it is recognized that the use of specific ARV drugs can be associated with change in serum lipid profiles in pattern that are known to pose increased risk for development of comorbidities (NCCDs).

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