

**FUNCTIONAL LIMITATION, HIV INFECTION, AND
MORTALITY IN AIDS LINKED TO THE INTRAVENOUS
EXPERIENCE (ALIVE) STUDY**

by

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ABSTRACT

As the results of HARRT, HIV has developed into a chronic disease where the incidence of age-associated disorder is rising. Functional limitation is reported to be associated with multiple adverse conditions in elderly HIV-infected individual. However, few studies have been conducted on health related quality of life, especially the effect of physical limitation on mortality in an HIV setting. The objectives of our study are to identify the correlates of functional limitation and the impact of functional limitation on mortality in a cohort of aging injection drug users (IDUs).

Functional limitation is ascertained as reporting “limited a lot” with any of the 6 physical activity questions contained in MOS-HIV and SF-12 questionnaires. Our study population contain 1854 participates from ALIVE Study recruited in 1988-1989, 1994-1995, 1998, 2000, and 2005-2008. GEE-logistic model is performed to assess the marginal effect of covariates on self-reported functional limitation. Kaplan-Meier survival analyses and Cox proportional hazards regression models were conducted to evaluate the impact of functional limitation on mortality.

208 deaths were observed in 1854 patients during a period of 6 years. The prevalence of functional limitation is 28% and HIV infected is 30%. In the multivariable model HIV infection is associated with an increased likelihood of being functional limited (OR, 1.20; 95% CI, 1.03–1.39). The association is stronger in person with advanced HIV disease (CD4 cell counts less than 350 cells/uL as well as detected viral load). Gender, age, education, number of comorbidity conditions and self-rated bodily pain and general health status is significantly correlated to functional

limitations. In survival analysis, functional limitation independently is associated with a dramatic decline (HR, 1.64; 95% CI, 1.25–2.16), in survival rate. But the effect is mediated by other variables such as sociodemographic factors, such as HIV status and comorbidity conditions (adjusted HR, 1.26; 95% CI, 0.93–1.71).

From the study we can conclude that HIV infection is associated with increased risk of functional limitation in IDUs populations. Individuals with advanced HIV disease have the highest risk of developing functional limitation. Functional limitation alone is associated with mortality, while the effect is mediated by other covariates.

This thesis is original, unpublished, independent work by the author, Hao Ying, under the supervision of Professor Greg D Kirk.

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INTRODUCTION

Since the use of highly active antiretroviral therapy (HAART), HIV has evolved to a chronic disease. According to the estimation of the Centers for Disease Control and Prevention (CDC), more than 1.1 million people in the United States are living with HIV at the end of 2010 and among those 19% are older than 50 years old. This figure has been increased by two fold since 1990. [1] Plenty of data have shown that even with proper medical care, individuals living with HIV have substantially decreased life expectancy and increased risk of comorbidity conditions compared to HIV-uninfected individuals with similar risk profile. [2, 3] Growing concerns have risen regarding of promoting the health status in people living with HIV/AIDS.

Functional limitation includes any health conditions that prevent a person from simple or complex activities, ranging from vigorous movement to basic activities of daily living (ADL). Functional limitation is of special interest because it reflects multiple clinical and subclinical diseases.[19] It can lead to the increasing risk of adverse clinical outcomes such as hypertension, obesity, diabetes, cardiovascular disease and arthritis.[5,6,7,9] It is also proven to be associated with risk behaviors like smoking, alcohol use and injected drug use.[4, 8] Furthermore, many studies suggest that HIV disease progression measured by CD4 cell counts [10,11,12] and HIV viral load [13] have been correlated to a decrease in physical activity in HIV-infected populations. Functional limitation is frequently measured as self-reported.

Africa America populations, especially black women, are more vulnerable in developing functional limitations. [14-17] Injected drug users are also among the most

disadvantaged subgroups in United States with greater risk of adverse conditions due to inaccessibility of social resources and high burden of drug-use-related healthy problems.

However, few studies have been conducted on health related quality of life, especially the effect of physical limitation on mortality in HIV-infected IDUs. The objectives of our study are to identify the correlates of functional limitation, and assess the impact of functional limitation on mortality in a cohort of aging injection drug users (IDUs).

METHODS

Study Populations

AIDS Linked to the IntraVenous Experience (ALIVE) Study is designed to study the natural history of HIV/AIDS in predominantly Africa America and Injection Drug User (IDU) populations. The study population contains 1854 participants older than 18 years old, recruited prospectively in 1988-89, 1994-1995, 1998, 2000, and 2005-2008 with written informed consent, among those 553 are HIV infected. [5,18] The ALIVE study is approved by the Johns Hopkins Institutional Review Board (IRB).

Data Collection

Starting from 2000, The MOS-HIV and SH-12 quality of life instruments was administrated to the 1854 participants. At their baseline visits, participants provided information on sociodemographic characteristics, physical activity, smoking, alcohol

use, injected drug use and self-rated bodily pain and health-related quality of life. HIV antibody was detected in HIV-uninfected populations using enzyme-linked immunosorbent assay (ELISA), and confirmed by western blot. HIV-infected individuals were tested for CD4 cell counts using flow cytometry, and plasma HIV-1 RNA levels tested using reverse-transcriptase PCR methods. The detection threshold of HIV viral load was less than 50 copies/ml. HAART treatment was defined as the use of at least 3 antiviral drugs, including one non-nucleoside reverse transcriptase inhibitor, in prior 6 months. Follow-up visits were administered every 6 months with ascertainment for physical activity, tobacco, alcohol and injected drug use, as well as tests for HIV antibody, CD4 cell counts and HIV viral load. Comorbidity conditions were ascertained as self-reported diagnosis of diabetes, strokes, hypertension, heart problem or chronic lung disease. Obesity was measured as having a body mass index (BMI) greater than 30. Self-rated general health status was categorized as 5 groups: excellent, very good, good, fair and poor. And self-rated bodily pain was considered as 6 groups: none, very mild, mild, moderate severe and very severe. Mortality was ascertained through linkage to the National Death Index (NDI), and confirmed by death certificates. [5]

Functional Limitation Assessment

Functional limitation was ascertained by asking participants impairments of the following items from MOS-HIV and SH-12 questionnaire: Vigorous activities (e.g., lifting heavy objects, running, sports); Bending, lifting or stooping; Climbing several flights of stairs; Moderate activities (e.g., pushing a vacuum cleaner, bowling,

golf); Walking one block; Eating, dressing, bathing, or using the toilet (Categorized as 1= Not limited; 2=Limited, 3=Limited a lot). Functional limitation was defined as having reported “limited a lot” in one of these items in prior 6 months, and was recorded as binary variables (0=Not limited; 1=Functional limited).

Data Analysis

Pearson χ^2 tests were used to test the difference of patient characteristic between HIV-positive and negative groups for variables like gender, race, education, risk behaviors, functional limitation and comorbidity conditions. GEE-logistic model was used to assess the marginal effect of sociodemographic, behavioral, and clinical variables on self-reported functional limitation. To evaluate the impact of functional limitation on all-cause death, Kaplan-Meier survival curves and Cox proportional hazards regression models were performed. The index visits were treated as the first record visit since 2005/1/1. Subjects were censored when death or reaching at the end of year 2011. Survival curves were constructed at the period of 6 years, until the year of 2011. Except for missing data, 1704 participants were included in the final model. The cox regression model was tested for proportional hazard assumption and was valid.

In both analyses, age was treated as continuous variables. Race was dichotomized as Africa Americas or not since the study population was predominantly Africa America. Commodity conditions have been combined into three categories: no commodity conditions, 1-2 commodity conditions and more than 3 simultaneously. To capture HIV progression status, “HIV advanced” variable has been created into 3

groups: HIV-negative, HIV not advanced (positive, CD4 cell counts less than 350 cells/uL or viral load undetected), and HIV advanced (positive, CD4 counts more than 350 cells/ml and viral load detected).

RESULTS

Patients and characteristics

The median age of the total 1894 participants was 46.5 years (IQR, 42.0, 54.7), 33% were female and 81% were Africa America. HIV-infected individuals accounted for 30% of the study population, with median CD4 cell counts of 304 cells/uL (IQR, 168, 464), and median HIV log₁₀ viral load of 3.05 copies/ml (IQR, less than 1.70, 4.46). HARRTs were used by 50% of the HIV-infected individuals during the index visits. According to Table 1, HIV-infected populations had similar age distributions as the general population, with a median age of 46.5 years (IQR, 42.0, 50.8) among HIV-infected and 45.7 years (IQR, 39.2, 50.9) among HIV-uninfected. A greater percentage of HIV-infected individuals are Africa America ($P<0.01$). The prevalence of comorbidity conditions was similar among HIV-infected when compared to general populations.

Risk Factors and Functional limitation

At index visits, 38% of the study population has reported “limited a lot” with any of the six activities listed above. Limitation in “vigorous activities” was the most common one with a prevalence of 28%; while the fewest percentages (only 7%) of participants reported impairment in performing “eating, dressing, bathing, or using the

toilet” (Table 2). Age and HIV status has been associated to the prevalence of functional limitation. The odds of functional limitation were 1.26 times higher in younger HIV-positive individuals, 1.34 times higher in older HIV-negative individuals, and 1.47 times higher in participants who were older and HIV-infected. Women tended to report functional limitation more frequently than men (43% versus 35% and P value<0.01) (Figure 1).

Risk factors regarding self-reported functional limitation were shown in Table 3 using both unadjusted and adjusted models. In the unadjusted model, older in age, being female, less than high school education, homeless, HIV-infected, having poorer self-rates health status and more severe bodily pain, and increasing number of comorbidity conditions were associated with higher risk of reporting functional limitation. After adjusting, almost all the risk factors retained their significance except for being homeless and having more than 3 comorbidity conditions. HIV infections were associated with 1.2 times greater risk of functional limitation (OR, 1.20; 95% CI, 1.03–1.39). Behavioral risk factors including tobacco use, alcohol use and injected drug use were not shown to have a significant impact on functional limitation (Table3, Model A). Further analysis regarding HIV disease progression suggested an observed difference (HR 1.19 vs. 1.30) in relations between functional limitations and advanced HIV disease (CD4 counts more than 350 cells/ml and viral load detected) when compared to HIV-infected control group (without advanced disease) (Table3, Model B & C).

Functional limitation and mortality

208 deaths were observed before 2011/12/31 in 1854 participants, among those 138 were male, and 70 were female. Overall functional limitation decreased patients' chance of survival (Log-rank test, P value <0.01) (Figure 2). Functional limitation together with HIV infection can lead to an even lower survival curve (Log-rank test, P value <0.01) (Figure 3). Functional limitation alone was associated with 0.64 times increasing likelihood of mortality (HR, 1.64; 95% CI, 1.25–2.16), but no longer significantly (HR, 1.26; 95% CI, 0.93–1.71) after adjusting for sociodemographic variables; alcohol, tobacco and drug use; HIV status; and number of comorbidity conditions (Table 4, Model A). We observed a stronger association of functional limitation with all-cause mortality in women (HR, 1.44; 95% CI, 0.85–2.45) than men (OR, 1.15; 95% CI, 0.79–1.68), although neither of them was statistical significant. It seemed that the impact of functional limitation on mortality can be explained by the joint effects of the variables listed above. Advanced HIV disease can strongly predict mortality with more than 4-fold higher risk (HR, 4.54; 95% CI, 3.18–6.47). However, it was not likely to interact with functional limitation because it did not change the coefficient of functional limitation very much (Table 4, Model A).

DISCUSSION

The reason of age-associated increase of functional limitation may come from three sources: biological aging (primary aging), lifestyle changes at advanced ages (secondary aging), and disease caused by aging (tertiary aging). [19] Our data shows that the biological effects still play a role after adjusting for behavioral risk factors

and comorbidity conditions. Each single comorbidity condition is not significantly associated with functional limitation. However, when combined into one variable (number of comorbidity conditions), it becomes meaningful in predicting functional limitation. Although groups with more than 3 comorbidity conditions finally lost their significance in the final model, it may be because of the tiny sample size (N=52). Our results indicate that a treatment for common comorbidity conditions may be helpful to prevent the incidence of functional limitation. Besides, there is no enough evidence that behavioral change (secondary aging), such as smoking, alcohol use or injected drug use, can cause self-reported functional limitation.

Consistent with prior studies, we discover that gender and education predict functional mortality.[14-17] The prevalence of functional limitation is higher in women than men. The reason may be social as well as biological. Firstly, female gender is associated with multiple chronic diseases in older age. When adjust for these variables, its effect on functional limitation attenuated.[14] Furthermore, being female is associated with low income and less education, both of which is the risk factors of functional limitation.[14] Finally, women may be more sensitive to and ready to accept bodily pain and discomfort, while men tend to ignore them. Thus, women are likely to have a lower threshold of reporting functional limitation than men.[20] Being more than high school education has protective effects on developing functional limitation because higher education leads to increasing attention in personal health status and healthy life style.

HIV infection can lead to increased likelihood of reporting functional

limitation. Even patients with well-controlled HIV disease have a significantly higher likelihood of developing functional limitation. Subjects with advanced HIV disease suffer from an even higher risk of functional limitation. Surprisingly, being treated by HAART fails to show protective effects compared to HIV-infected without HAART. Our data shows that there are still 38% of the person-visits under HAART suffering from advanced HIV disease. The reason affects the effectiveness of HAART in HIV-infected IDUs may be captured as following: 1. Late diagnosis of HIV infection can cause low CD4 cell counts before implementing HARRT. 2. Lack of accessibility of medical care in IDUs. 3. Unwillingness to take drugs and lack of adherence to HAART drugs. [5,21,22,23] Focusing on the effectiveness of HARRT, especially improving the adherence in IDU population is of great importance in reducing the incidence of functional limitation.

There are several limitations in our study: 1. Measurements of functional limitation can be refined for further accuracy and reliability. Since the prevalence of single functional limitation items are quite different from each other, ranging from 28% to 7%. They should not be put onto a same weight. Individuals with only “vigorous activities” limitation may not be as equal as individuals with impairment in “eating, dressing, bathing, or using the toilet”. More complicated algorithm may be used to more accurately capture patients’ physical activity profile. 2. The study population is mainly IDUs and Africa America, so the study’s generalizability might be limited. 3. Most of the variable (functional limitation, diagnosis of comorbidity conditions, self-rated bodily pain and general health status) are ascertained by

self-reporting and will be subjected to reporting bias.

In summary, our study finds out that functional limitation independently is associated with a dramatic decline in survival rate. However, the effect is mediated by the joint effected of sociodemographic factors, HIV status and comorbidity conditions. Number of comorbidity conditions and advanced HIV disease are strongly associated with rising chance of mortality. Correlates of functional limitation included gender, education, age, HIV status, number of comorbidity conditions and self-rated bodily pain and general health status.

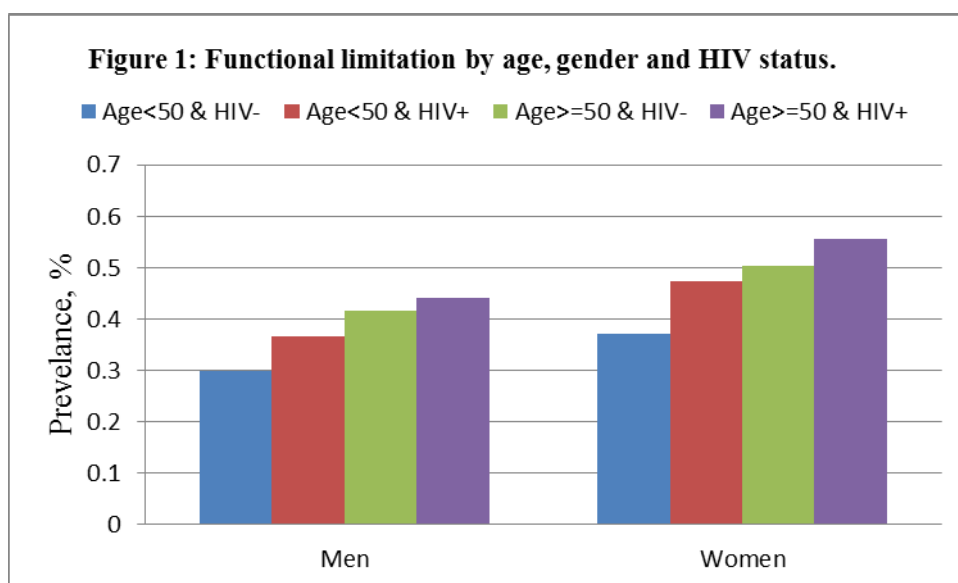
Table 1: Characteristics of 1854 ALIVE Participants, by HIV Status.

	HIV infected n=(553)	HIV uninfected n=(1301)	P value
Age in years			
<40	23.0%	31.7%	<0.01
41-50	55.9%	42.4%	
>50	21.2%	25.8%	
Women	36.4%	32.2%	0.084
African American	90.1%	76.6%	<0.01
Average income (per half year)			
None	22.1%	25.4%	0.305
\$0-5000	54.0%	52.5%	
>\$5000	23.9%	22.1%	
Less than high school education	63.1%	55.1%	<0.01
Homeless	21.7%	30.2%	<0.01
Current Cigarette Smoker	83.9%	86.3%	0.170
Alcohol use in last 6 month	53.8%	65.1%	<0.01
IDU in last 6 month	54.6%	64.9%	<0.01
Comorbidity conditions			
Obesity	16.5%	20.5%	0.060
Diabetes	2.4%	1.8%	0.406
Strokes	0.7%	0.5%	0.482
Hypertension	11.3%	9.9%	0.364
Heart problem	2.2%	1.8%	0.565
Chronic lung disease	2.6%	1.6%	0.180
HIV+ Populations			
CD4 count, median	304		
Viral load, log10 copies/ml, median	3.05		
Recent HAART	49.9%		

Table 2: Prevalence of functional limitation in study population.

	HIV infected n=(553)	HIV uninfected n=(1301)	P value
Function limitations^a			
Vigorous activities	31.5%	26.6%	0.033
Bending, lifting or stooping	19.7%	18.5%	0.550
Climbing several flights of stairs	22.2%	18.5%	0.060
Moderate activities	18.6%	15.8%	0.140
Walking one block	12.1%	10.6%	0.343
Eating, dressing, bathing, or using the toilet	7.8%	7.2%	0.635
Total number of functional limitations			
None	57.1%	64.2%	0.162
One	16.1%	12.8%	
Two	8.5%	6.8%	
Three or more	18.3%	16.2%	

^aFunctional limitations prevalence is defined as having experienced self reported "limited a lot" in individual activities from 2005 to 2010



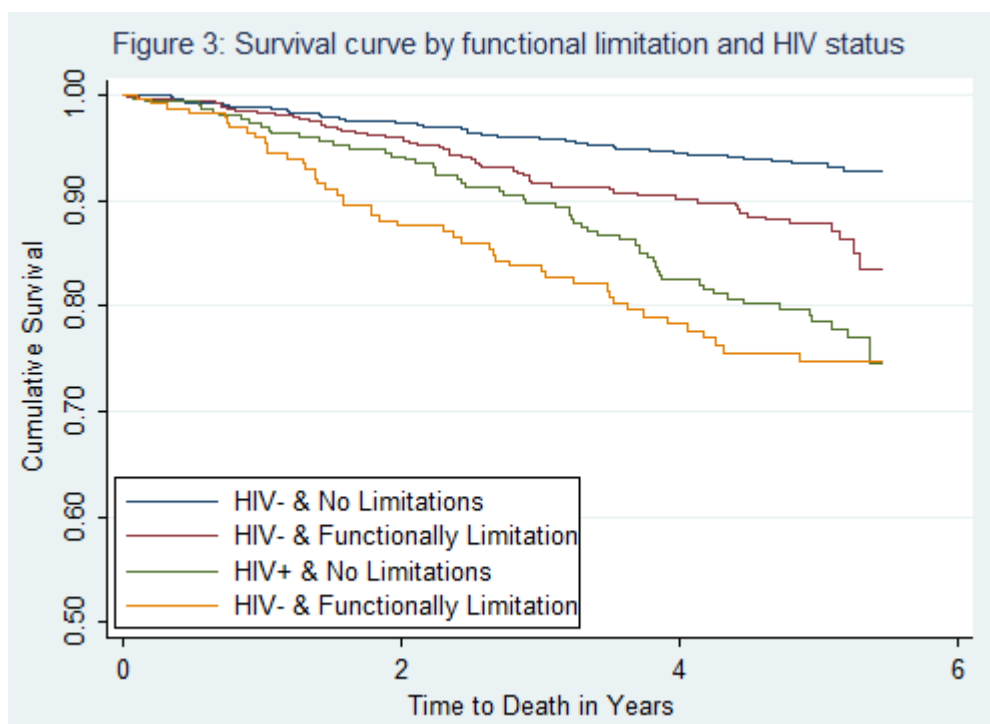
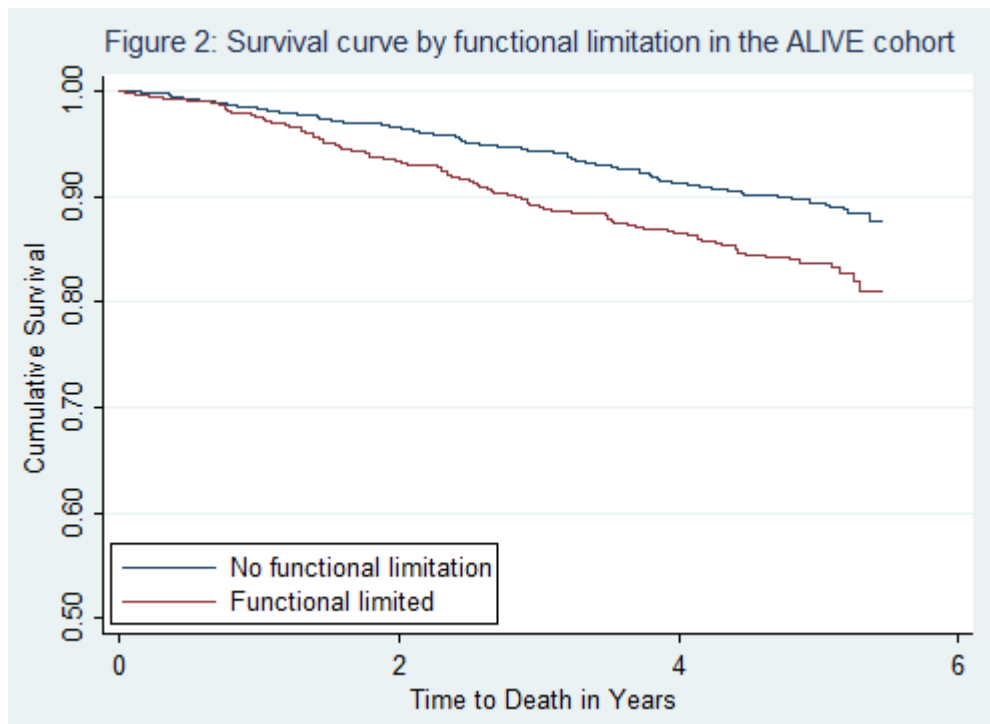


Table3: Odds of Functional Limitation by Sociodemographic, Behavioral, and Clinical Risk Factors

Variables	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Model A^a				
Age ^d	1.03	1.02-1.05	1.03	1.02-1.04
Female	1.37	1.19-1.58	1.27	1.10-1.47
Africa America	1.02	0.84-1.23		
Education ^c	0.75	0.65-0.86	0.73	0.63-0.84
Homeless	1.12	1.01-1.25	1.10	0.98-1.23
Current tobacco use	1.08	0.96-1.22		
Current alcohol use	1.07	0.98-1.17		
Current injected drug use	1.04	0.96-1.13		
HIV positive	1.22	1.05-1.41	1.20	1.03-1.39
Self-rated bodily pain	1.40	1.35-1.44	1.36	1.31-1.40
Self-rated general health status	1.29	1.23-1.34	1.12	1.06-1.18
Comorbidity conditions				
0	Ref		Ref	
1-2	1.33	1.21-1.47	1.26	1.14-1.40
More than 3 (n=52)	1.63	1.02-2.63	1.34	0.80-2.24
Model B^b				
HIV status				
HIV negative	Ref		Ref	
HIV not advanced	1.18	1.00-1.40	1.19	1.01-1.41
HIV advanced	1.36	1.14-1.62	1.30	1.09-1.56
Model C^b				
HIV status				
HIV negative	Ref		Ref	
HAART	1.20	1.03-1.46	1.20	1.00-1.43
No HAART	1.21	1.02-1.43	1.21	1.02-1.44

^aAdjusted for age, gender, education, homeless, HIV status, bodily pain, general health status, score, and # of comorbidity conditions.

^bAdjusted for age, gender, education, bodily pain, homeless, general health status score and # of comorbidity conditions.

^cCategoried as less than high school or higher.

^dAs continuous variables.

Table 4: Mortality Risk associated with Functional Limitation and HIV among ALIVE Participants.

Variables	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Model A^a				
Functional limitation	1.64	1.25-2.16	1.26	0.93-1.71
Age	1.05	1.03-1.07	1.06	1.04-1.08
Female	1.01	0.76-1.35	0.96	0.69-1.33
Africa America	1.52	0.99-2.32	0.82	0.51-1.32
Education ^c	0.88	0.67-1.17	1.00	0.74-1.35
Current tobacco use	1.00	0.68-1.47		
Current alcohol use	0.99	0.75-1.31		
Current injected drug use	0.87	0.66-1.14	1.16	0.85-1.57
HIV positive	2.74	2.09-3.60	2.87	1.22-7.59
Number of comorbidity ^e				
0-1	Ref		Ref	
2	1.18	0.86-1.61	1.11	0.80-1.53
More than 3	3.82	1.56-9.34	3.04	1.22-7.50
Model B^b				
Functional limitation	1.64	1.25-2.16	1.27	0.94-1.73
HIV status				
HIV negative	Ref		Ref	
HIV not advanced	1.85	1.31-2.61	2.05	1.43-2.95
HIV advanced ^d	4.49	3.25-6.20	4.54	3.18-6.47

^aAdjusted for age, gender, race, education, current IDU, HIV status, blood albumin, bodily pain, general health

^bAdjusted for age, gender, race, blood albumin, general health status and # of comorbidity conditions.

^cCategorized as less than high school or higher.

^dHIV advanced defined as both CD4 < 350 and with detected viral load.

^eComorbidity conditions include obesity, diabetes, heart problem, strokes, chronic lung disease and hypertension.

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Curriculum Vita

The author Hao Ying was born in October 5th 1989, in China. He got a bachelor degree of science while training for biological science in Fudan University, China. After that he studied epidemiology as Master of Science in Johns Hopkins Bloomberg School of Public Health concentrated on infectious disease. He has done research assistants with skills at data extraction, management and analysis using multiple computing software. He has been involved in the public health internships with a background in biochemistry, genetic engineering and molecular biology. Primary research interests include HIV infection, comorbidity and aging.