



Published in final edited form as:

*AIDS Behav.* 2020 June ; 24(6): 1592–1598. doi:10.1007/s10461-019-02635-0.

## Successful functional aging in middle-aged and older adults with HIV

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### Abstract

People living with HIV (PLWH) experience greater everyday functioning impairment. We examined frequency and correlates of successful functional aging (SFA) in PLWH. Using gold-standard questionnaires, SFA was defined in 174 HIV+ and 71 HIV- adults as absence of significant everyday cognitive symptoms and declines in instrumental activities of daily living. More HIV- (45%) than HIV+ (18%) adults met SFA criteria ( $p < 0.01$ ). Depression, cognitive functioning, socioeconomic status, and HIV status were independent correlates of SFA ( $p$ -values  $< 0.05$ ). Motor ability, learning, and verbal fluency were associated with SFA. SFA was associated with health-related quality of life (HRQoL). PLWH are three times less likely to achieve SFA than HIV- adults, a phenotype that translates to HRQoL. While SFA is multifactorial, driven by clinico-demographic factors, HIV may pose additional risk to achieving SFA. Further work should examine other mechanisms whereby HIV hinders SFA (e.g., biomarkers, stress, mental health) and ultimately inform interventions to facilitate SFA.

### Keywords

everyday functioning; daily functioning; activities of daily living; HIV/AIDS; social determinants

### Introduction

As individuals are living longer with HIV, the need to examine the effects of HIV disease in the context of aging is paramount. Older people living with HIV (PLWH) experience greater levels of a host of physical<sup>1,2</sup>, cognitive<sup>3,4</sup>, and emotional<sup>5,6</sup> comorbidities than their seronegative counterparts. All of these factors can increase the risk for worse everyday functioning, disability, poorer health outcomes, and lower quality of life among older PLWH. Indeed, studies show additive effects of HIV and aging in multiple areas of everyday functioning capacity and manifest status, including basic and instrumental activities of daily living<sup>7</sup> and vocational functioning<sup>8</sup>. In fact, impairment in everyday functioning may occur

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in over 50% in older PLWH<sup>9</sup>. Further, estimates from a large study suggest that nearly half of US PLWH received disability benefits, which was nine-fold higher than observed in seronegatives<sup>10</sup>.

Yet, there is ostensibly a subset of older PLWH who not only avoid functional disability, but are thriving and achieve successful everyday functioning outcomes. Identification and clinical characterization of such “successful functional agers” among PLWH may provide valuable insights for developing cognitive, behavioral, emotional, and physical interventions to promote positive everyday functioning and health outcomes. This effort is informed by the growing number of studies examining successful aging in various clinical domains (e.g., physical, cognitive) among PLWH, with heterogeneity in the definitions and operationalizations used. As in the larger aging literature, the construct of successful aging varies widely in HIV, but generally aims to represent those PLWH with the highest level of functioning. These definitions have ranged from those focusing on subjective, patient-centered definitions to those including broad and global operationalizations as well as more domain-specific phenotypes such as positive psychological factors (e.g., resilience) and neurocognition (e.g., optimal subjective and objective cognitive functioning). For example, studies of successful cognitive aging - as defined by absence of objective neurocognitive deficits and subjective cognitive complaints - have shown that only approximately 20–30% of PLWH present with this phenotype as compared to approximately 30–50% of seronegative counterparts<sup>11,12</sup>. Among older PLWH, successful cognitive aging is associated with better everyday functioning outcomes, including fewer declines in activities of daily living<sup>11</sup>, better health behaviors (e.g., medication management)<sup>11</sup>, positive psychological factors<sup>13</sup>, and higher quality of life<sup>12</sup>.

Thus the aim of this study was to determine the frequency and clinical correlates of successful functional aging (SFA) in PLWH. That is, are HIV+ adults and older adults less likely to present with successful functional outcomes than their HIV-negative counterparts? Although positive psychological factors and neurocognition play a role in functional aging in HIV, they are neither necessary nor sufficient in predicting functional disability. Such understanding of this end of the spectrum of functioning in PLWH will ultimately help to identify potentially modifiable correlates of such outcomes. Importantly, little work has examined this topic in the Deep South, which has become an epicenter of the HIV/AIDS epidemic and reflects a unique demographic from the cohorts prevailing in the neurobehavioral HIV/AIDS literature (e.g., New York City, Southern California), particularly in terms of higher burden of those of lower socioeconomic status (SES) and African Americans. Thus, the purpose of the current study was to examine the prevalence of SFA in a cohort of HIV+ and HIV-negative adults and older adults in the Deep south. Further, we examined demographic, health, psychological, and neurocognitive correlates of SFA. Finally, we examined the association between SFA and quality of life outcomes in PLWH.

## Materials and Method

### Participants and Procedure

Two hundred forty-five participants were included in the current study (n=174 HIV+ and n=71 HIV-). HIV+ participants were recruited from a University HIV/AIDS Clinic. A brief telephone screen determined eligibility, which included the following: no major conditions that may affect neurocognitive functioning (e.g., Schizophrenia, Alzheimer's disease), no gross sensory deficits, no head injury with loss of consciousness longer than 30 minutes, and not currently undergoing chemo or radiation therapy. The only difference between HIV+ and HIV- participants in enrollment criteria was a 40+ age cutoff was used for HIV+ participants while 50+ was used for HIV- participants. While age 50 is often used as the cutoff in studies pertaining to aging-related issues in PLWH, the parent study from which these data were derived employed a 40+ cutoff for several reasons: 1) the prevalence of HAND is higher in middle-aged and older PLWH than their younger counterparts, 2) using a younger cutoff allowed more variability in age to examine in analyses, 3) given that cognitive declines in fluid abilities may begin in the 40's in PLWH, examining correlates of cognitive and functional outcomes from a life course perspective may be advantageous, particularly with regard to identifying early indicators of decline and implications for interventions. After providing written, informed consent, enrolled participants completed a comprehensive battery including neurocognitive and everyday functioning measures. Table I displays the sample's clinicodemographic characteristics.

### Measures

**Sociodemographics**—Sociodemographics were gathered via a self-report questionnaire and included: age, sex, race/ethnicity, years of education, and yearly household income (i.e., 1 = \$0-\$10,000 to 11 = \$100,001 and above). Verbal IQ was estimated from the reading subtest of the Wide Range Achievement Test-4th Edition (WRAT-4;<sup>14</sup>). Given the conceptual overlap and collinearity between education, income, and verbal IQ (mean Pearson's  $r=.56$ ), a SES composite was created as the sample-based z-score of those three variables for use in analyses.

**Successful functional aging**—Successful functional aging (SFA) was assessed with two gold standard self-report everyday functioning measures. Instrumental activities of daily living (IADL) declines were measured using the Heaton version of the Lawton and Brody (1969) scale (Heaton, Marcotte, et al., 2004; Woods et al., 2008). Participants rated current abilities compared to previous levels of functioning across 12 domains: housekeeping, home repairs, laundry, managing finances, managing medications, shopping, buying groceries, cooking, working, transportation, understanding written material/television, and using the telephone. Total number of IADL declines was derived as a continuous score (possible range: 0–12). The Patient's Assessment of Own Functioning Inventory (PAOFI) was used to measure perceived cognitive symptoms in everyday life across the domains of memory, language and communication, use of hands, sensory-perceptual, higher level cognitive and intellectual function, and work (if applicable) (Chelune, Heaton, & Lehman, 1986). The scale includes 34 items with Likert-type scale responses: "Almost always", "Very often", "Fairly often", "Once in a while", "Very infrequently", and "Almost never". Items endorsed

as “fairly often” or greater were classified as “significant” cognitive symptoms. The primary outcome on the PAOFI was the number of significant everyday cognitive symptoms (possible range: 0–34). Participants with zero IADL declines (56% of sample) and one or fewer cognitive symptoms (37% of sample) were classified as SFA+ (26% of sample), while persons not meeting both of those criteria were classified as SFA- (74% of sample).

**Neurocognitive functioning**—Neurocognitive functioning was assessed via a comprehensive, seven-domain, gold-standard neurocognitive battery (Woods 2004)<sup>15,16</sup>. Raw test scores were converted to demographically-corrected T-scores using the most appropriate normative corrections<sup>17</sup>. Neurocognitive impairment (NCI) was defined using the published clinical ratings approach, such that those with a global clinical rating of 5 or greater (which is indicative of at least two cognitive domains in the impaired range) were classified as impaired<sup>18</sup>. Global clinical ratings were used in analyses while the NCI classification was used for descriptive purposes.

**Clinical Variables**—HIV characteristics were derived from interview and clinic records and included current and nadir CD4 count, plasma viral load, treatment status (on/off), and estimated duration of HIV disease. All participants provided urine samples for toxicology (TransMed®) for the following illicit substances: amphetamines, methamphetamine, opiates, and cocaine. The Center for Epidemiological Studies Depression Scale (CES-D; <sup>19</sup>) was used to assess depressive symptomology and scores of 16 or greater were categorized as clinically relevant. Comorbidities were assessed via a self-report health questionnaire.

**Quality of life**—Within the HIV+ sample, health-related quality of life (HRQoL) was assessed with the Medical Outcomes Study HIV Health Survey (MOS-HIV)<sup>20</sup> which is a well-validated 35-item measure assessing 10 dimensions of HRQoL (i.e., general health perceptions, physical functioning, role functioning, pain, social functioning, mental health, energy/fatigue, health distress, cognitive functioning, and quality of life). Scores on each of these dimension scales are used to calculate overall physical health summary (PHS) and mental health summary (MHS) scores using standardized criteria<sup>21</sup>.

## Analyses

The primary model was a logistic regression in which HIV serostatus was used to predict SFA group. In order to determine covariates for the model, we first compared the HIV groups on demographic and clinical variables listed in Table I using t-tests or chi square tests when appropriate. Similarly, the SFA groups were examined for differences in the variables listed in Table I. All variables that were associated with either HIV status or SFA were entered into a nominal logistic regression predicting SFA, along with HIV status. Finally, within the HIV+ group, multivariable analysis of variance (MANOVA) was used to examine the association of SFA with the PHS and MHS HRQoL scores, using a similar covariate selection approach as mentioned above. A critical alpha of .05 was used throughout. All analyses were conducted in JMP Pro version 14.

## Results

HIV+ and HIV- groups differed on age, gender, race, and SES ( $ps < .05$ ). Clinical variables were largely similar between groups ( $ps > .05$ ), with the exception that the HIV+ group had significantly more individuals with clinically relevant depressive symptomatology ( $p < 0.01$ ). At the univariate level, the HIV- group had significantly more individuals meeting the criteria for SFA (45%) than the HIV+ group (18%) (odds ratio (OR) = 3.64, 95% confidence interval (CI) = 1.99 – 6.67,  $p < 0.01$ ). Regarding correlates of SFA in the full sample, the following emerged: the SFA+ group was significantly more likely to be older and white, have higher SES and lower global clinical ratings (i.e., better cognitive functioning) and less likely to have depressive symptoms ( $ps < .05$ ). A multivariable logistic regression in the overall sample including age, gender, race, SES, depressive symptoms, and global clinical ratings showed that SES, depressive symptoms, and global clinical ratings remained independent correlates of SFA ( $ps < 0.05$ ) while age ( $p = 0.19$ ), gender ( $p = 0.16$ ), and race ( $p = 0.64$ ) were not retained. A follow-up analysis modeling HIV status along with these three significant correlates showed that all variables were significant independent correlates of SFA ( $ps < 0.05$ ) (Table II). Univariate analyses between individual domain ratings and SFA among the HIV+ sample showed that those with SFA had significantly lower domain ratings (better performance) in motor function (Cohen's  $d = 0.42$ ,  $p = 0.04$ ). Statistical trends with comparable effect sizes emerged in the domains of verbal fluency (Cohen's  $d = 0.40$ ,  $p = 0.05$ ) and learning (Cohen's  $d = 0.35$ ,  $p = 0.08$ ).

Given that 41% of the HIV+ sample was aged 40–49, we conducted a sensitivity analysis comparing those HIV+ aged 50+ ( $n = 103$ ) to the HIV- sample ( $n = 71$ ). These results were consistent with those in the larger sample. The same serostatus group differences emerged as with the full HIV+ sample: the HIV+ 50+ group was on average significantly younger, more likely to be non-white and male, had lower SES, and was more likely to be depressed than the HIV-group ( $ps < .05$ ). At the univariate level, the HIV- group had significantly more individuals meeting the criteria for SFA (45%) than the HIV+ group (20%) (OR = 3.20, 95% CI = 1.64 – 6.26,  $p < 0.01$ ). As with the serostatus differences, the same differences by SFA status emerged in the 174 subjects aged 50+: the SFA+ group was significantly more likely to be older and white, have higher SES and lower global clinical ratings (i.e., better cognitive functioning) and less likely to have depressive symptoms ( $ps < .05$ ). A multivariable model showed that depressive symptoms and HIV status were significant correlates of SFA ( $ps < 0.05$ ).

Finally, we examined the association of SFA with HRQoL in our HIV+ sample. First we conducted separate linear regressions for PHS and MHS that included variables associated with SFA (i.e., age, SES, race, depression, global clinical ratings). These analyses determined that depression and global clinical ratings would be entered as covariates in the following MANOVA. The mixed model MANOVA including depression, global clinical ratings, SFA, and the SFA x HRQoL interaction as the independent variables and PHS and MHS as the within-subjects dependent variables showed main effects of both depression and SFA on HRQoL ( $p < 0.001$ ). The SFA x HRQoL was not significant ( $p = 0.13$ ), suggesting that the magnitude of the association between SFA and HRQoL is similar for both physical and mental HRQoL.

## Discussion

With the aging of the HIV population, greater understanding of the intersection of age and HIV on outcomes is necessary. Indeed, studies show that older HIV+ adults exhibit poorer daily functioning than their younger and seronegative counterparts. Over the course of the epidemic, research has evolved from focusing on risk factors for poor outcomes, to isolating protective factors whereby a subset of PLWH avoid such functional disability, which may mirror those found in the normal aging literature. The goal of this study was to examine prevalence of SFA in HIV+ adults as compared to HIV seronegative adults and to determine correlates of this phenotype.

We found that HIV+ adults were three times less likely to achieve SFA than HIV- adults. This difference remained even when accounting for important socio-clinical factors that were associated with both HIV status and SFA status, including SES, depression, and cognitive functioning. This suggests that HIV confers additional risk that may prevent some PLWH from experiencing SFA. This expands prior work demonstrating everyday functioning dysfunction in PLWH by suggesting that this population is also less likely to achieve optimal daily functioning as operationalized as absence of everyday cognitive symptoms and IADL declines and dependence using validated instruments commonly applied in the neuroAIDS literature. These lower rates of SFA in our HIV+ group are similar, although somewhat lower than in prior studies of successful cognitive aging in PLWH. This suggests that SFA may be a particularly difficult outcome to achieve in the context of HIV disease.

These results suggest that SFA is multifactorial, with contributions from psychosocial and neuropsychiatric factors. Our findings yielded similar sociodemographic and psychological correlates that have been found in studies predicting everyday functioning and successful cognitive aging in PLWH<sup>11,12,15,22</sup> as well as without HIV<sup>23,24</sup>. These included higher SES, better mood, white race, and better cognitive performance. Interestingly, physical health and disease indices were not associated with this SFA phenotype. Prior work on other successful aging operationalizations in PLWH (e.g., successful cognitive aging)<sup>11-13</sup> have also demonstrated no associations between disease severity and such outcomes, which may be driven by largely healthy samples, but may also suggest the importance of examining non-HIV biomarkers in the ART era, such as those included in the Veterans Aging Cohort Study (VACS) Index (e.g., renal functioning, Hepatitis C status)<sup>25</sup>.

There may be several other unexamined variables that may explain the independent association of HIV of SFA beyond the clinic-demographic variables included in this study. Recent work examining trauma, economic hardship, and stress in PLWH showed that these contextual factors were associated with everyday functioning in PLWH but not in seronegative adults<sup>26</sup>. Thus while we demonstrated an independent effect for SES in the current study, additional examination of related factors may have explained additional variance in SFA. Furthermore, while we found a clear association of depressive symptoms with SFA, a more granular examination of specific components of depression (e.g., somatic) as well as broader aspects of negative affect (e.g., anxiety, apathy) may provide a clearer understanding of how mental health hinders SFA. Indeed, apathy is prevalent in PLWH<sup>27,28</sup>



and shows a consistent association with everyday functioning<sup>28,29</sup> and quality of life<sup>30</sup> in this population over and above psychiatric disorders. Furthermore, aspects of personality such as conscientiousness may play a role in SFA, perhaps via greater compensatory mechanism use and tendencies towards better organization and goal attainment that are important for successful execution of daily activities. In Alzheimer's disease for example, low conscientiousness has shown independent associations with impairment in performance of IADLs, above and beyond demographics and cognitive dysfunction<sup>31</sup>.

Our finding that global cognitive functioning emerged as an independent predictor over and above demographics and depression was also consistent with prior work in PLWH as well as in the larger aging literature and speaks to the multifactorial mechanisms contributing to SFA. Further exploration of individual cognitive domains that may have been driving this effect showed that motor function as well as verbal fluency and learning may contribute to SFA. Regarding the motor findings, prior studies have shown that even mild extrapyramidal dysfunction is associated with IADL dependence and lower quality of life among older HIV + adults<sup>32,33</sup>. Similarly, recent work in PLWH has focused on the frailty phenotype and suggests this factor may confer risk for poorer everyday functioning<sup>34</sup> and less successful aging<sup>35</sup>. Our finding that fluency was a correlate of SFA also supports existing work demonstrating that executive dysfunction is associated with IADL dependence<sup>32,33</sup>. For example, it has been suggested that impaired action fluency, an indicator of impaired frontal systems, may adversely affect IADL functioning via disruption of cognitive scripts needed to successfully perform IADL tasks. Similarly, our finding that poorer functioning in learning may hinder SFA further supports the role of frontal systems in everyday functioning, including prior work showing the influence of this domain on IADL dependence particularly among older PLWH, which may be driven by shallow encoding and consolidation<sup>36</sup>.

Finally, we found that SFA showed an independent association with HRQoL in PLWH even when accounting for mood and cognitive status. Further, these associations were similar for both physical and mental HRQoL, which suggests that SFA is an equally important driver of both outcomes. This supports prior work in PLWH highlighting the association of successful aging and HRQoL. However, these prior studies of successful cognitive aging showed that this phenotype was uniquely associated with mental HRQoL but not physical<sup>12,13</sup>. Thus our findings support that SFA is both scarce in PLWH and is associated with two important and distinct downstream HRQoL outcomes. Development and testing of interventions targeting either SFA indicators (e.g., mood, cognitive functioning) or SFA itself (e.g., compensatory strategies<sup>37</sup>, assistive devices) are warranted in order to ultimately protect HRQoL in PLWH. Further work is also needed to understand the predictive role of SFA on other endpoints (e.g., falls/injury, mortality).

While this study provides novel insights on a clinically relevant phenotype in PLWH, several limitations should be noted. These include lack of HIV seronegative adults in the 40–49 age range, although this likely did not have a biased effect on our findings, as our analyses did consider age and our sensitivity analysis including only those HIV+ aged 50+ also yielded similar results to the full sample. Further, our available data did not allow for characterizing HIV risk behaviors in our HIV- sample, thus future studies should include HIV- “at-risk”

populations and examine how factors such as impulsivity, risk behaviors, and pre-exposure prophylaxis (PrEP) might influence of SFA. Next, while our operationalization of SFA was based upon gold-standard and valid measures of everyday functioning commonly used in the HIV/AIDS literature, and recent evidence supports concordance between such self-report measures and objective measures<sup>38</sup>, nonetheless future work examining the SFA phenotype would benefit from a combination of objective and subjective measures of daily functioning. Indeed, affective state<sup>39</sup> and metacognitive awareness<sup>40</sup> may influence self-report measures of daily functioning. Finally, the cross-sectional nature of our study did not allow for examination of SFA trajectories, which may shed light on both predictors and maintenance of this outcome.

## Acknowledgments

This study was supported by National Institutes of Health (NIH) grants K99/R00-AG048762 (PLF), R01-MH106366 (DEV), P30-AG022838, and R24-AI067039.

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**Table 1.**

Sample Descriptives for N=245 HIV+ and HIV- Adults and Older Adults

	HIV+ (n=174)	HIV- (n=71)	
<b>Demographics</b>			
Age	51.30 (7.03)	61.00 (7.22)	<0.01
Aged 50+	59%	100%	<0.01
Gender (% Male)	62%	46%	0.03
Race (% White) <sup>a</sup>	14%	44%	<0.01
Years of education	12.56 (2.16)	13.96 (2.64)	<0.01
Verbal IQ	88.63 (14.22)	98.38 (18.28)	<0.01
Income	1.94 (1.62)	3.83 (3.04)	<0.01
<b>Clinical Variables</b>			
Diabetes (% with)	18%	15%	0.73
Stroke (% with)	4%	3%	0.79
Hypertension (% with)	57%	59%	0.80
High Cholesterol (% with)	38%	39%	0.65
Urine screen (% positive for drugs) <sup>b</sup>	28%	17%	0.10
Estimated years with HIV	16.74 (8.43)	--	--
Antiretroviral therapy (% on) <sup>c</sup>	91%	--	--
Viral load (% undetectable) <sup>d</sup>	66%	--	--
Current CD4 <sup>e</sup>	644.40 (364.43)	--	--
Nadir CD4 <sup>f</sup>	254.48 (260.89)	--	--
Depressive symptoms (% with)	49%	19%	<0.01
Neurocognitive impairment (% with)	53%	41%	0.07
<b>Successful Functional Aging Variables</b>			
Successful Functional Aging (% Yes)	18%	45%	<0.01
IADL Declines = 0 (% Yes)	51%	69%	<0.01
PAOFI total 1 (% Yes)	30%	54%	<0.01

Note.

<sup>a</sup>97% of HIV+ and 98% of HIV- non-White were African American<sup>b</sup>n=170 HIV+ and n=58 HIV-, drugs include meth, amphetamines, opiates, and cocaine<sup>c</sup>n=169<sup>d</sup>n=146<sup>e</sup>n=124<sup>f</sup>n=157.

**Table II.**

Logistic Regression Estimates (N=245)

<b>Dependent Variable: Successful Functional Aging</b>				
<b>Independent Variables</b>	<b>B(SE)</b>	<b>Lower 95% CI</b>	<b>Upper 95% CI</b>	<b>p-value</b>
Socioeconomic Status	0.15 (0.07)	0.02	0.29	0.02
Global Clinical Rating	-0.25 (0.12)	-0.50	-0.03	0.03
Depressive Symptoms (Depressed)	-0.64 (0.20)	-1.05	-0.27	0.01
HIV Status (HIV-)	0.36 (0.18)	0.01	0.71	0.04

**Note.** CI=confidence interval, B=beta coefficient, SE=standard error.

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