Bachelor's thesis

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Prevalence, and Sociodemographic, Medical and Psychological Predictors of Neurocognitive Impairment in Iranian People With HIV: An Exploratory Cross-Sectional Study

Bachelor's thesis in Psychology PSY2900
Supervisor: Maede S. Etesami
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Preface

The initial part of the bachelor project was in large part designed and completed by my supervisor Maede Sadat Etesami. The data had already been collected before I joined the project in January 2023. My supervisor gave me a thorough and detailed recount of the sampling of participants and data collection, as well as provided background literature on HIV-associated NCIs and overview of the HIV epidemic in Iran. Additional literature was found within the database known as 'Google Scholar'; searches were done with key words such as: NCI, HIV, HIV-associated neurocognitive disorder (HAND), and Iran. My contribution to the project consists of pooling relevant literature, running the analyses, interpreting the results, and writing the thesis. My supervisor suggested that I choose exploratory hypotheses due to the vast scope of the collected data, and also suggested appropriate statistical analyses should I choose an exploratory approach. The choice, however, was mine to make. The student assistant was a big help with questions related to the statistical analyses and APA guidelines. My supervisor and student assistant have been readily available for questions for the duration of the project and have continuously provided good feedback. My fellow student has also been a steady support in confirming my interpretations and conclusions, as well as providing psychosocial support. I declare that my bachelor thesis is an independent work of my own.

I wish to further acknowledge the contribution of the research participants, as without them the research would not have been possible. I also want to thank Imam Khomeini Hospital Complex for providing a location for the execution of the study, as well as providing necessary medical history of the participants when needed. I want to give a special thanks to Maede Etesami, Ingvill Holmen Tangen, and my fellow student, for their aforementioned continuous support throughout the project. Finally, I want to give my thanks for the opportunity to join in on an interesting project that provided good learning opportunities.

Abstract

Between 30-60% of people with HIV (PWH) worldwide struggle with neurocognitive impairments (NCIs). In Iran, there are over 50 000 PWH. Currently, the prevalence of HIV-associated NCIs in Iran is not well documented. This exploratory cross-sectional study aimed to determine the prevalence of impairments in Iran and discover sociodemographic and medical risk factors associated with poorer neurocognitive functioning in PWH compared to a control group consisting of Iranian people without HIV (PWoH). Based on ROC curve cut off scores calculated from Iranian norms, the prevalence of impairments was 59% and 19% for PWH and PWoH, respectively. A stepwise hierarchical linear regression analysis revealed that identifying as female and being married negatively predicted cognitive function in Iranian PWH, while CD4+ T-cells/mm^3 was found to be a positive predictor. Higher premorbid IQ and being single were found to be significant predictors of higher cognitive function in PWoH. The analysis of covariance (ANCOVA) with age, gender, premorbid IQ, levels of education, and marital status as covariates found that the PWH performed significantly worse than PWoH in global neurocognitive functioning, non-verbal learning, planning, and two out of three subtests of attention. There were no group differences detected in visual memory and selective attention; however, those analyses did not have enough power to detect meaningful effects. Future studies could implement looser exclusion criteria to increase the sample size and thus statistical power. Looser exclusion criteria could also allow future studies to investigate whether neurocognitive ageing is related to NCIs in Iranian PWH.

Prevalence, and Sociodemographic, Medical and Psychological Predictors of Neurocognitive Impairment in Iranian People With HIV: An Exploratory Cross-Sectional Study

Ever since the acquired immunodeficiency syndrome (AIDS) epidemic in the 1980s, human immunodeficiency virus (HIV) infection has affected over 30 million people in the world (Nightingale et al., 2014). The introduction of antiretroviral therapy (ART) has resulted in an otherwise fatal disease to become a manageable, chronic disease (Grant, 2008). One of the consequences of an increased life expectancy is that the people with HIV (PWH) have to live with chronic, non-fatal symptoms over an increased amount of time. One of these symptoms is HIV-associated neurocognitive impairment (NCI). NCI in PWH has a prevalence of 30-60% worldwide (Haddow et al., 2018; Heaton et al., 2010; Kato et al., 2020; Wright et al., 2008; Zenebe et al., 2023).

In Iran, there are over 50,000 PWH and the numbers increase with over 4,000 a year (Najafi et al., 2020; Seyedalinaghi et al., 2021). Early in the HIV epidemic in Iran, the group most vulnerable to HIV infection were people who injected drugs (PWID) (Najafi et al., 2020). The first occurrence of a major HIV outbreak in PWIDs in Iran was in 1996, and shared needles when injecting drugs remained the most common route of transmission in Iran until a report of the Iranian Ministry of Health identified that sexual contact accounted for 45% of new HIV infections (Najafi et al., 2020). Additionally, newer infections show a shift in transmission trends from men to women (Seyedalinaghi et al., 2021). Since 2000, multiple voluntary counselling and testing (VCT) centres have been established in Iran (Seyedalinaghi et al., 2021), which can be found in health centres, blood banks, and rehabilitation centres all over the country (Najafi et al., 2020). The VCT centres provide access to and administer ART free-of-charge to PWH (Seyedalinaghi et al., 2021). Several HIV positive clubs have been

established and provide psychosocial support to PWH and their friends and family (Najafi et al., 2020; Seyedalinaghi et al., 2021).

The current largest obstacle in Iran's HIV response is proposed to be HIV diagnosis. In 2018 it was estimated that for Iranian PWH, only 36% were aware of their positive serostatus (Seyedalinaghi et al., 2021). Given an estimated total population of 59 000 Iranian PWH (Seyedalinaghi et al., 2021), that leaves 37 760 unaware and untreated PWH. 20% of the PWH who were aware of their serostatus was estimated to be on ART (Seyedalinaghi et al., 2021). However, since July 2017, Iran has implemented a "HIV test and treat" strategy in VCT centres, which, along with stigmatisation interventions, have been proposed to improve the positive-to-ART treated ratio (Seyedalinaghi et al., 2021). As far as we are aware, not much research has been devoted to NCIs in Iranian PWH. Based on global findings, it is likely that NCIs are affecting thousands of ART treated Iranian PWH and reducing their life quality drastically.

An NCI is usually defined as a significant deficit in two out of six neurocognitive domains: attention and working memory; executive function and abstraction; speed of processing; memory, including learning and recall; sensory-perceptual and motor skill; and verbal learning and memory (Alford & Vera, 2018). Research shows that in pre-ART treated PWH, motor skills, cognitive speed and verbal fluency were the predominant deficient cognitive domains (Heaton et al., 2011). However, in PWH on active ART, the affected domains tend to be executive functioning, attention, and memory (Grant, 2008; Heaton et al., 2011). The Frascati criteria categorise an NCI in three different levels of severity of dysfunction, based on the degree of the deficits in the domains and reported interference with daily functioning (Grant, 2008). In this study, however, NCIs are decided based on a receiver operating characteristic (ROC) curve cut-off score calculated from mean T-scores of each neurocognitive test in the battery in an Iranian sample found in Etesami et al. (2022). In this

way, the NCIs could be determined from local norms instead of American norms, which would reduce possible confounding cultural differences.

Neurocognitive decline in PWH seem to be associated with the viral load of HIV RNA in cerebrospinal fluid (CSF) and plasma. CSF viral escape is the term coined for the occurrence when HIV RNA is detectable in the CSF, yet undetectable in plasma (Alford & Vera, 2018). Some studies indicate a connection between CSF viral escape and NCIs in PWH, as detectable levels of HIV RNA in CSF has been shown to be associated with HIV associated NCIs (Nightingale et al., 2014). In general, treatments that suppress viral load in plasma and have a low degree of CSF viral escape are generally accepted as effective (Santos et al., 2019). ART's main function is to suppress the level of HIV RNA in the CSF and plasma, as well as ensure rejuvenation of CD4+ T-cells (Santos et al., 2019). The HIV infection attacks the CD4+ T-cells and directly and indirectly deplete the amount of healthy CD4+ T-cells in the central nervous system (CNS; (Casaletto et al., 2017). CD4+ T-cells/mm^3 is associated with the severity of the HIV infection progression, where levels lower than 200/mm^3 are diagnosed as AIDS. As well as reducing the probability of developing AIDS, some studies show that ART diminishes the severity of the NCIs affecting the PWH (Maschke, 2000; Nightingale et al., 2014). As it stands, ART treated PWH suffer from less severe yet chronic NCIs, and more research dedicated to NCIs in the ART-era can help improve life quality of millions of PWH.

To the best of our knowledge, NCI in Iranian PWH is not explored enough. Thus, the aim of this study is to contribute to the growing volume of research dedicated to NCI in PWH in the ART-era, specifically in Iran. Firstly, we want to identify the prevalence of NCIs in Iranian ART treated PWH and in Iranian people without HIV (PWoH). We hypothesise that there will be a significant difference in NCI prevalence between PWoH and PWH. This study follows a purely exploratory approach and thus aspires to investigate possible risk factors with

as little preconceptions as possible. Previous research on NCIs identify age, gender, years of education, IQ, ethnicity, marital status, CD4+ T-cells/mm^3, years of HIV infection duration, and affective illnesses such as depression and anxiety, as risk factors (Atashili et al., 2013; Grant, 2008; Haddow et al., 2018; Heaton et al., 2010; Wei et al., 2020; Wright et al., 2015; Zenebe et al., 2023). These findings have influenced what variables are included in the sociodemographic and medical questionnaire, and the psychological measurements. Additionally, to avoid possible confounders on the relationship between NCIs and and HIV-associated risk factors, we wished to control for variables that have documented effects on neurocognitive function, such as history of traumatic brain injuries, coinfections, substance and alcohol dependence, and psychiatric pharmacology (Franke et al., 2014; Kolson, 2022; McIntosh et al., 2021; Saloner et al., 2019; Shrestha et al., 2017; Wortzel & Arciniegas, 2014; Yakasai et al., 2017). The intention of applying strict exclusion criteria is to isolate, as much as possible, our observations to characteristics specific to Iranian PWH. The main aim of this study is to explore the possible predictive associations between sociodemographic, medical, and psychological variables and neurocognitive function in PWH and PWoH. Lastly, the study aims to identify any significant group differences in cognitive functioning in the neurocognitive domains executive functioning, attention, and memory, between the PWoH and the ART treated PWH.

Method

Ethical Considerations

All study participants provided written informed consent. This research was approved by the Tehran University of Medial Sciences Ethics Committee (Registration code: IR.TUMS.VCR.REC.1396.3323), the Iran University of Medical Sciences Ethics Committee (Registration code: IR.IUMS.REC.1396.30893) and it was conducted in accordance with the Declaration of Helsinki.

Procedures and Design

The study was conducted in the VCT centre of Imam Khomeini Hospital Complex in Tehran, Iran between August 2017 and January 2019. It was made up of two parts, one consisting of an interview phase with a pen and paper demographic and medical questionnaire supervised by two psychologists, and one testing phase with a computerised neurocognitive test battery supervised by a licensed psychologist. If participants were unfamiliar with digital tools, they went through a group workshop for computer skills. All appointments for the testing phase were between 9 AM and 12 PM. Participants were not allowed to smoke or drink caffeinated beverages due to possible decreases or increases in alertness and cognitive flexibility (Camfield et al., 2014) during the neurocognitive tests, and their blood sugar level was controlled (Donohoe & Benton, 1999) by serving breakfast and snacks. The neurocognitive tests were conducted in a sealed room with darkened lights and suppressed acoustics on anti-reflective monitors to control for possible distraction due to their self-reflection during the cognitive tests. The order of the tests was the same for all participants and the tests were interspersed with 10-minute breaks. The average completion time of the entire test battery was 90 minutes.

Participants

200 PWH and 124 PWoH were interviewed by two trained psychologists. PWH who were visiting the VCT centre were offered to join the study. All PWH between 18 and 50 years old who had been confirmed infected with HIV by the hospital-supervised Enzyme-Linked Immunosorbent Assay (ELISA) test at least 2 years preceding the study, who were currently on ART, had no history of a CD4+ T-cell count < 200/mm^3 and central nervous system opportunistic infections, and are fluent in Farsi were eligible for the study. If their antiretroviral drug prescription included Efavirenz (EFZ), then the PWH were required to have been on the treatment for longer than six months to minimise the possible

neuropsychiatric difficulties which can have an effect on neurocognitive functioning, such as dizziness and attention deficits within the first 6 months of use (Giancola et al., 2018). PWoH were matched to the best, and paired in sociodemographic characteristics, such as mean of monthly income and residence within the same districts of the city. Most PWoH were sampled from people visiting the blood donation centres in the Imam Khomeini Hospital Complex. The PWH and PWoH were not gender matched because less women tend to donate blood than men, due to physical differences that prohibit women from donating blood (e.g., menstruation) (Kasraian et al., 2021) and the heavy stigmatisation of HIV for women in Iran (Shirpak et al., 2007). Thus, the PWH group has an equal gender distribution, whereas the PWoH group has a male majority. This study followed, as much as possible, the Sex and Gender Equity in Research (SAGER) guidelines for women and minorities, and transgender participants were registered under their self-reported gender.

Exclusion criteria for all participants, based on factors that may influence cognitive performance, included history of traumatic brain injury as defined by the DSM-V criteria (Wortzel & Arciniegas, 2014)*;* comorbidities such as cardiovascular and cerebrovascular disease and diabetes (McIntosh et al., 2021); alcohol or drug dependence, as defined by the DSM-V criteria, within the last 2 years (Shrestha et al., 2017); current psychiatric pharmacotherapy (i.e., SSRIs, benzodiazepines, or ADHD stimulant medications, such as Ritalin) (Franke et al., 2014; Kolson, 2022; Saloner et al., 2019); history of or active hepatitis C virus (HCV) co-infection (Yakasai et al., 2017); and uncorrected auditory or visual deficits (Roberts & Allen, 2016). After applying inclusion and exclusion criteria, the final sample (*N* = 126) consisted of 63 PWH and 63 PWoH.

Materials

Sociodemographic, Medical and Psychological Measurements

Demographic and Medical Questionnaire. Sociodemographic measures were assessed with a Farsi self-report questionnaire. The questionnaire was made up of questions about age, self-reported gender (dichotomous male/female) marriage status (married, single, widowed, divorced-separated), ethnicity (Fars, Kurdish, Turkish, Lor, other), years or level of completed education (less than 12 years at school, high school diploma, two years of university education, bachelor's degree, master's degree, PhD, other), drug use over the past 2 years (dichotomous yes/no), drug use at one point in life (dichotomous yes/no), smoking (dichotomous yes/no). Some items were transformed in the following analyses, due to varying responses, see Statistical Procedure further down. The medical measures consisted of questions of transaction route (drug injection, sexual, received contaminated blood from blood transmission, other, don't know), years since HIV diagnosis, years on ART, CD4+ T-cell/mm^3, and history of Hepatitis C (dichotomous yes/no). The medical measures were confirmed through their medical records.

Raven Standard Progressive Matrices. Premorbid IQ was assessed with the Raven Standard Progressive Matrices (SPM), which consists of five sets of increasingly difficult 12 items each (Raven, 2003). The RSPM can be applied to a wide variety of ages, spanning from young children to the elderly. It is non-verbal in its design, and is therefore used to study intelligence worldwide (Matzen et al., 2010). Retest-reliabilities lie between r_{tt} = .83 and r_{tt} = .93, and correlations with other intelligence tests have values varying between r = .20 to r = .80 (SCHUHFRIED GmbH, 2023).

Beck Depression Inventory-Short Form. Depression scores were measured using the Beck Depression Inventory-short form (BDI-SF), a 13-item version of the longer Beck Depression Inventory (BDI). The BDI-SF correlates strongly with BDI, with correlations ranging from r = .89 to r = .97 (Beck et al., 1974). The Farsi translation has an internal validity of α = .89 (Rajabi, 2005) and has been documented as a reliable and valid

psychometric measurement of depression in Iran (Dadfar & Kalibatseva, 2016). The cut-off score for moderate and more severe depression, for optimal sensitivity, should lie at 13 (Furlanetto et al., 2005).

Beck Anxiety Inventory. Anxiety scores were assessed with the Beck Anxiety Inventory (BAI), a 21-item self-report test with high internal reliability $\alpha = .92$. A cut-off of a score of 36 can be used for distinguishing severe anxiety from less severe mood illnesses (Beck et al., 1988). Both the BDI-SF and BAI were translated to Farsi.

Neurocognitive Measurements

To measure the neurocognitive function the subjects completed a computerised neurocognitive test battery from the Vienna Test System (VTS). The neurocognitive test battery used in this study assessed 4 out of the 6 cognitive domains commonly affected by NCI: attention and working memory; executive function and abstraction; speed of processing; memory, including learning and recall (Alford & Vera, 2018). Verbal memory and learning tests were not included in the battery because the Farsi translation of the language tests were not available in the VTS. Additionally, a *t*-score which represented the general neurocognitive functioning, called global neurocognitive function (GCF), was calculated by averaging the six tests' *t*-scores into a mean *t*-score. The presence of NCIs was decided based on a ROC curve calculated from *t*-scores of an Iranian sample found in Etesami et al. (2022) for all six tests and the GCF. Table 1 summarises what domain the tests that make up the test battery measures, as well as their internal reliabilities and ROC curve cut off scores.

Table 1

Overview of Neurocognitive Tests, Reliability and ROC Curve Cut-Off Scores

Test	Domain	Reliability[a]	ROC cut-off[b]
Global neurocognitive function	All domains	N/A	39.4
Non-verbal learning test	Memory: learning and recall	.80 - .90	47
Tower of London – Freiburg-version	Executive function and abstraction (planning)	> .70	34
Visual memory test	Memory: learning and recall	.64 - .84	61
Divided attention	Attention and working memory	.96 - .97	31
Spatial attention and visual field test	Attention and working memory; Speed processing	.88 - .97	35.33
Selective attention	Attention and working memory; Speed processing	.94 – .97	36

Note. [a]Measured as Cronbach's Alpha (α)

[b]Iranian cut-offs calculated by ROC curve, found in Etesami et al. (2022)

Non-verbal Learning – Short Form. The memory domain was assessed with the Non-verbal Learning Test – short form (NVLT), which is comprised of 120 items. The respondents were presented a figure of irregular lines or a regular geometric figure for three

seconds, after which the respondents had to decide whether they had seen the figure before or not. Eight figures were presented five times in the short version. Higher *t*-scores indicate better performance. Internal reliability values for NVLT falls between $\alpha = .80$ and $\alpha = .90$ (Sturm & Willmes, 2011).

Tower of London – Freiburg Version. The executive function and abstraction domain was assessed using the test Tower of London – Freiburg version (TOL-F). Executive function and abstraction were here condensed into testing the participant's ability to make and execute a plan. The respondent is presented a digital three-dimensional wooden model with three rods and three balls (coloured red, yellow and blue), where the rods can hold from one, two or three balls. The participants are asked to move the three balls from a starting state to a goal state, which is presented in the upper part of the screen. Additionally, the participants should solve the digital puzzle in as few moves as possible, and the number of minimum moves needed to solve the puzzle is displayed during the test. TOL-F aims to measure the respondent's ability to plan and act out an action. The internal reliability of TOL-F, which consisted of 28 items, lies above $\alpha = .70$ (Kaller et al., 2011). This domain will also be described as the planning domain interchangeably.

Visual Memory Test. The memory domain was further assessed with the participants ability to learn and recall visual cues. The 14-item version of the Visual Memory Test (VISGED) was utilised in this study. The test is comprised of a simple city map with visual symbols which mark locations the respondents are supposed to memorise. After a short inoculation period, the map reappears without the symbols, and the participants are asked to give an approximation of the location of several of the memorised symbols. Higher scores indicate better performance. Internal reliability of the VISGED test varies between $\alpha = .64$ and $\alpha = .84$ (Etzel & Hornke, 2018).

The attention and working memory domain was measured by three different tests developed to measure sub-functions of attention: Divided Attention Test (WAFG), Spatial Attention and Visual Field Test (WAFR), and Selective Attention Test (WAFS). All scores for the attention subtests are based on *t*-scores transformed from reaction times, where shorter reaction times was translated into higher *t*-scores. Therefore, higher scores indicate better performance for all attention tests (Sturm, 2011a, 2011b, 2011c).

Divided Attention Test. Divided Attention Test studies the participants ability to split their attention between dual tasks, by presenting them with stimuli in two different sensory channels (Sturm, 2011a). The channels could consist of two visual channels, or one auditory and one visual. In both versions of the test, the participants are asked to react if one channel of stimuli "lightens" (if visual) or "softens" (if auditory) twice in succession. The auditory and visual version of the test was utilised in this study. The internal reliability is high and falls between, $\alpha = .96$ and $\alpha = .97$ for Divided Attention Test (Sturm, 2011a).

Spatial Attention and Visual Field Test. Spatial attention, on the other hand, measures the participants' subfunction of attention related to spatial orienting. Spatial orienting revolves around, for the most part, the ability to shift one's attention from one spatial stimulus to a new spatial stimulus (Sturm, 2011c). The respondents have to react to changes in a visuo-spatial environment, one of four black arrows changing colour, by pressing a button. At random intervals, the change will be preceded by either a false or true cue of the incoming change. The test both monitors the participants' response times and their error rates. The internal reliability of Spatial Attention and Visual Field Test lies between, $\alpha = .88$ and $\alpha = .97$ (Sturm, 2011c).

Selective Attention Test. The final sub-function of attention measured in this study is selective attention, which is recognised as the ability to focus attention on given features of a task whilst suppressing irrelevant features (Sturm, 2011b). The Selective Attention test is a

choice reaction test, where the respondents are asked to react if a circle or square lightens or darkens, and to not react to changes in a triangle. Similar to the WAFR, the test measures the response times and the error rates. The internal reliability falls between, $\alpha = .94$ and $\alpha = .97$ for the selective attention (Sturm, 2011b).

Both spatial attention and selective attention can be viewed as indirect measures of the cognitive domain speed of processing. Although the tests were developed to measure attention, they also serve as measurements of participants' response times and as such speed processing.

Statistical Procedures

Analyses were performed using IBM SPSS Statistics version 28 and MedCalc Software Ltd. Comparison of proportions calculator. To test the first hypothesis of group differences in NCI prevalences, MedCalc's comparisons of proportions calculator was utilised. For the initial analyses of correlations between sociodemographic, medical and psychological variables and GCF, Pearson's correlation and Spearman's correlation were utilised to identify significant correlates. The significant correlates were further included in two stepwise hierarchical regression linear analyses: one for PWH and PWoH respectively. There was not made a distinction between variables that were only correlated with GCF in one group, as this would allow for comparisons of strength and directions of predictions in GCF scores between the groups. In other words, if one variable was only significantly correlated with GCF in either PWH or PWoH it was included in both regression analyses. The first block in both regression analyses consisted of variables that were not correlated with each other, and for each new model only one variable was added to investigate the contribution of that predictor to the model as a whole. Lastly, all significant correlates were controlled for in ANCOVAs to investigate the group differences in neurocognitive function performance scores in all six tests and GCF.

Due to lacking responses in some of the items for education and marital status, some items were combined to ensure enough statistical power. For education, the categories two years at university, bachelor's degree, master's degree and PhD were combined into a joint category: higher education. The category "other" had no responses. For marital status, the categories single, widowed, and divorced-separated were combined into the joint category unmarried.

Results

Participant Characteristics

63 PWH and 63 PWoH were included in the final analysis. Sociodemographic and medical variables are summarised in Table 2. The mean age of the participants was 35 and the majority of the participants were male (64%). The PWoH consisted of 46 men (73%) and 17 women (27%). The gender distribution was more equal in the PWH group, as it consisted of 34 men (54%) and 29 women (46%). The PWoH were similar to the PWH except the PWoH were significantly more likely to have completed more than 12 years of education, be male, be younger; and were significantly less likely to smoke, to have used drugs previously, and be suffering from depression and anxiety. The majority of the PWH identified as Fars (40%), followed by Turkish (27%), Kurdish (10%), Lor (5%), and other (6%). The average HIV infection duration was 7.33 years, and the mean years of receiving ART was 5.54. The mean CD4+ T-cells/mm^3 was 550.73, the lowest count rested at 280 CD4+ T-cells/mm^3 and the highest was 943 CD4+ T-cells/mm^3. The most common route of HIV-acquisition was sexual (48%), followed by needle injection (18%), unknown (18%), other (10%), and receiving contaminated blood in blood transmission (5%).

Table 2

Descriptive Statistics of Sociodemographic and Medical Variables.

Variables	**PWH (*n* = 63)**	**PWoH (*n* = 63)**	***p***
Age [years], mean [min: max]	36.76 [22:50]	33.86 [19:50]	$t(124) = -2.09$, $p = .039$
Gender [male][a], *n* (%)	34 (54)	46 (73)	$X^2(1) = 4.87$, $p = .027$
Ethnicity [Fars][b], *n* (%)	31 (49)	30 (48)	$X^2(1) = 0.01$, $p = .911$
Marital status [married][c], *n* (%)	29 (46)	37 (59)	$X^2(1) = 2.12$, $p = .146$
Education [less than 12 years at school][d], *n* (%)	32 (51)	21 (33)	$X^2(1) = 4.17$, $p = .042$
Smoking [no][e], *n* (%)	47 (75)	45 (71)	$X^2(1) = 0.25$, $p = .615$
History of drugs [no][f], *n* (%)	45 (71)	57 (91)	$X^2(1) = 8.12$, $p = .004$
Depression, mean (*SD*)	7.36 (5.90)	4.37 (4.93)	$t(118) = -3.00$, $p = .003$
Anxiety, mean (*SD*)	10.66 (9.75)	6.05 (6.35)	$t(105.28) = -3.11$, $p = .002$
Premorbid IQ, mean (*SD*) [min:max]	91.08 (12.24) [69:111]	93.94 (16.90) [69:132]	$t(113.02) = 1.09$, $p = .279$
Route of HIV-acquisition [sexual][g], *n* (%)	30 (48)	N/A	N/A
CD4+ T-cells/mm^3, mean (*SD*) [min:max]	550.73 (186.15) [280:943]	N/A	N/A
Years since HIV diagnosis, mean [min:max]	7.33 [2:18]	N/A	N/A
Years on ART, mean [min:max]	5.54 [0:18]	N/A	N/A

Note. [a]Gender: 1 = male, 2 = female (transgender participants registered as self-reported gender).

[b]Ethnicity – for the PWH: Turkish = 17 (27%), Kurdish = 6 (10%), Lor = 3 (5%), and other 4 (6%); for the PWoH: Turkish =14 (22%), Kurdish = 8(13%), Lor = 6 (10%), and other = 2 (3%).

[c]Marital status: 1 = married, 2 = unmarried (includes single, widowed and divorced-separated).

[d]Education – in the PWH: high school diploma = 20 (32%), and higher education 11 (18%); in the PWoH: high school diploma =25 (40%), and higher education 16 (25%).

[e]Smoking: 1 = yes, 2 = no

[f]Drug dependence at one point in life: 1 = yes, 2= no

[g]Route of HIV-acquisition: needle injection = 12 (21%), received contaminated blood at hospital in 1985 = 3 (5%), other = 6 (10%), and don't know 11 (18%).

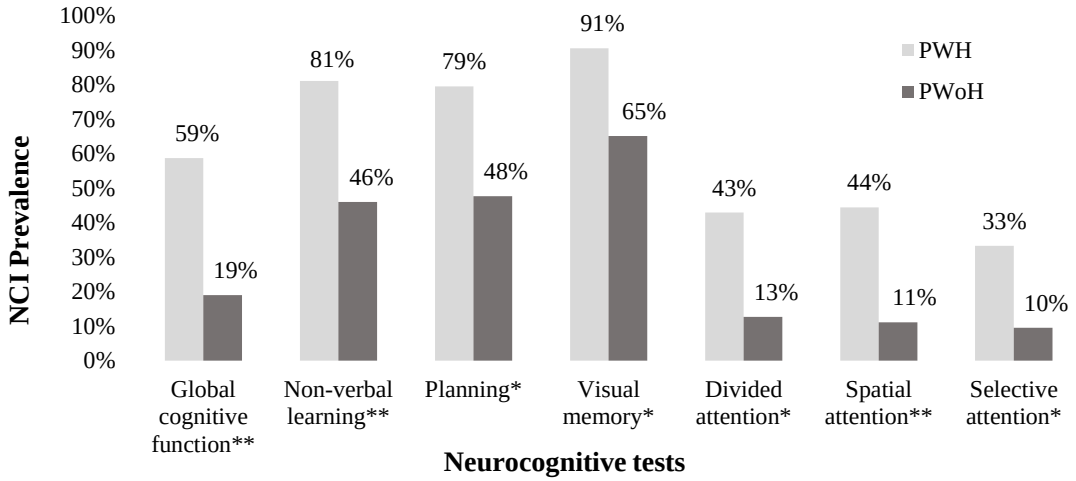
Prevalence of NCIs

The prevalence of NCIs in global neurocognitive function in the Iranian PWH was 59%, and the NCI prevalence for PWoH rested at a significantly, $p < .001$, lower 19%.

Furthermore, the largest percentage of NCIs for the PWH could be found in the visual memory domain, where the prevalence was 91%, with a significant, $p = .006$, difference between the PWH and the PWoH. The lowest prevalence was in selective attention, where the prevalence for NCIs in the PWH was 33%. The results from comparison of proportions analysis as well as a visual representation of NCI prevalence could be found in Figure 1.

Figure 1

Prevalence of NCIs for PWH and PWoH Groups in the Neurocognitive Tests, and Significance Results from Comparison of Proportions Analysis.



Note. *$p < .05$, ** $p < .001$.

Factors Associated with Global Neurocognitive Function

As shown in Table 3, Pearson's and Spearman's correlation analyses were performed to investigate the relationship between GCF and sociodemographic and medical variables for PWH. Scatterplots were investigated to ensure the assumption of linear relationships were met for Pearson's correlation analysis. Additionally, boxplots were examined to detect possible outliers, however, none were found. Lastly, Normal QQ-Plots indicated that all of the variables included in the Pearson's correlation analysis were normally distributed. For the

assumptions of Spearman's rho, scatterplots were examined to ensure that the assumption of a monotonic relationship was met. The results showed that premorbid IQ (M = 91.08, SD = 12.24) was significantly positively correlated with GCF, $r(61) = .38$, $p = .002$; additionally, CD4+ T-cells/mm^3 (M = 550.73, SD = 5.39) was also significantly positively correlated with GCF, $r(61) = .38$, $p = .002$. Identifying as female (M = 1.46, SD = 0.5) was significantly associated with lower GCF scores, $r_s(61) = -.40$, $p < .001$; and higher levels of education (M = 1.67, SD = 0.76) was significantly correlated with higher GCF performance scores, $r_s(60) = .51$, $p < .001$. Additionally, time since HIV diagnosis (M = 7.33, SD = 3.74) was neither associated with GCF $r(61) = -.05$, $p = .672$, nor CD4+ T-cells/mm^3, $r(61) = -.20$, $p = .111$.

As shown in Table 4, Spearman's rho and Pearson's r were utilised to examine the correlations between demographic and medical variables and GCF in PWoH. To test the assumption of linear relationship for the continuous variables, scatterplots were investigated. Furthermore, examining boxplots revealed no outliers. Normal QQ-Plots indicated that the continuous variables included in the Pearson's correlation analysis were normally distributed. For the assumption of monotonic relationship for Spearman's rho, scatterplots were examined. All assumptions were considered to be met. For the PWoH, premorbid IQ (M = 93.94, SD = 16.90) was significantly positively correlated with GCF (M = 44.14, SD = 5.40), $r(61) = .69$, $p < .001$; and age (M = 33.86, SD = 7.59) was significantly negatively correlated with GCF, $r(61) = -.32$, $p = .010$. Additionally, higher levels of education education (M = 1.91, SD = 0.77) was significantly positively correlated with GCF performance scores, $r_s(61) = .47$, $p < .001$; and being married (M = 1.41, SD = 0.50) was significantly associated with higher GCF scores, $r_s(61) = .37$, $p = .003$.

The variables age, premorbid IQ, gender, education, marital status and CD4+ T-cells/mm^3 were recognised as significant correlates and included in further analysis.

Table 3

Correlations Between GCF and Continuous and Categorical Variables for PWH

	Variable	***n***	***M***	***SD***	**GCF**
Continuous[a]					
	GCF	63	39.17	5.35	-
	Age	63	36.76	8.01	-.09
	Premorbid IQ	63	91.08	12.24	.38*
	Depression	61	7.36	5.91	.01
	Anxiety	62	10.66	9.75	-.11
	Time since HIV diagnosis	63	7.33	3.74	-.05
	CD4+ T-cells/mm^3	63	550.73	5.39	.38*
Categorical[b]					
	Gender	63	1.46	0.5	-.40**
	Education	63	1.67	0.76	.51**
	Ethnicity	61	2.07	1.26	-.09
	Drug	63	1.71	0.46	-.19
	Smoking	63	1.75	0.44	-.10
	Marital status	63	1.54	0.50	-.12

Note. *p < .05, ** p < .001

[a]Performed using Pearsons correlation analysis

[b]Performed using Spearman's correlation analysis

Table 4

Correlations Between GCF and Continuous and Categorical Variables for PWoH

	Variable	***n***	***M***	***SD***	**GCF**
Continous[a]					
	GCF	63	44.14	5.40	-
	Age	63	33.86	7.59	-.32*
	Premorbid IQ	63	93.94	16.90	.69**
	Depression	59	4.38	4.93	.12
	Anxiety	60	6.05	6.35	.04
Categorical[b]					
	Gender	63	1.27	0.45	.09
	Education	62	1.91	0.77	.47**
	Ethnicity	60	2.03	1.21	-.06
	Drug	63	1.90	0.30	.08
	Smoking	63	1.71	0.46	-.02
	Marital status	63	1.41	0.50	.37*

Note. *p < .05, ** p < .001

[a]Performed using Pearsons correlation analysis

[b]Performed using Spearman's correlation analysis

Predictors of Global Neurocognitive function

For further investigation of the relationship between the significant correlates and GCF, a stepwise hierarchical linear regression model was performed. Scatterplots were

investigated to test the assumption of linear relationships. Additionally, there were no significant outliers spotted in boxplots. Homoscedasticity was investigated by plotting standardised residuals against standardised predicted values, and the assumption of homoscedasticity was considered to be met. Finally, VIF and tolerance values were well within the normal limit, which indicates no multicollinearity (Field, 2018). Results from the stepwise hierarchical linear regression for the PWH are summarised in Table 5.

Age, premorbid IQ and gender (model 1) explained 31%, R^2_{adj} = .31, p < .001, of the variance in GCF. Gender was the strongest predictor, β = -.44, p <.001, followed by premorbid IQ, β = .36, p = .001. Age was not a significant predictor, β = -.08, p = .470.

The variance explained increased to 36%, ΔR^2 = .06, p = .021, R^2_{adj} = .36, p < .001, when education was added to the model (model 2). Identifying as female still predicted lower scores in GCF and gender was the strongest predictor, β = -.37, p < .001, followed by education, β = .31, p = .021. Premorbid IQ was no longer a significant predictor, β = .18, p = .154.

The variance explained in GCF increased to 40%, ΔR^2 = .05, p = .026, R^2_{adj} = .40, p < .001, when marital status was included in the model (model 3). Gender was the strongest predictor, β = -.44, p = .001, followed by premorbid IQ, β = .27, p = .036, marital status, β = -.25, p = .026. Education was not a significant predictor in model 3, β = .21, p = .131.

CD4+ T-cells/mm^3 was added to the final model (model 4), where the variance explained was 44%, ΔR^2 = .04, p = .033, R^2_{adj} = .44, p < .001. Identifying as female strongly predicted a decrease in GCF, β = -.42, p <.001, followed by being unmarried also predicting a lower GCF score, β = -.25, p = .022, and higher CD4+ T-cells/mm^3 counts predicted a small increase in GCF score, β = .22, p = .033. Neither age, β = -.16, p = .117; premorbid IQ, β = .24, p = .064; nor education, β = .17, p = .190, were significant predictors in the final model.

Table 5

Stepwise Hierarchical Linear Regression Model of GCF and Significantly Correlated Variables for PWH

Variable	***b*** ***[95% CI]***	SE_b	**β**	***p***	***F***	R^2_{adj}
Model 1				<.001	10.31	.31**
Age	-0.05 [-0.19, 0.09]	0.07	-.08			
Premorbid IQ	0.16* [0.06, 0.25]	0.05	.36*			
Gender	-4.73** [-6.98, -2.48]	1.12	-.44**			
Model 2				<.001	9.75	.36**
Age	-0.08 [-0.22, 0.06]	.007	-.12			
Premorbid IQ	0.08 [-0.03, 0.19]	0.06	.18			
Gender	-3.93** [-6.20, -1.66]	1.13	-.37**			
Education	2.18* [0.34, 4.02]	0.92	.31*			
Model 3				<.001	9.42	.40**
Age	-0.11 [0.24, 0.03]	0.07	-.16			
Premorbid IQ	0.12* [0.01, 0.23]	0.06	.27*			
Gender	-4.66** [-6.94, -2.37]	1.14	-.44**			
Education	1.44 [-0.44, 3.33]	0.94	.21			
Marital status	-2.68* [-5.03, -0.33]	1.17	-.25*			
Model 4				<.001	9.17	.44**
Age	-0.11 [-0.24, 0.03]	0.07	-.16			
Premorbid IQ	0.10 [-0.01, 0.21]	0.06	.24			
Gender	-4.46** [-6.67, -2.24]	1.11	-.42**			
Education	1.22 [-0.62, 3.06]	0.92	.17			
Marital status	-2.67* [-4.94, -0.39]	1.14	-.25*			
CD4+ T-cells/mm^3	0.01* [0.00, 0.01]	0.00	.22*			

Note. *p < .05, ** p < .001

Results from the stepwise hierarchical regression for the PWoH are summarised in Table 6. To test the assumption of linear relationships, we investigated scatterplots. No significant outliers were observed in the boxplots. The assumption of homogeneous variance was investigated by plotting standardised residuals against standardised predicted values, and

the assumption of homoscedasticity was met. Finally, no multicollinearity was indicated with VIF and tolerance values were within the normal limit (Field, 2018).

Table 6

Stepwise Hierarchical Linear Regression Model of GCF and Significantly Correlated Variables for PWoH

Variable	***b*** **[95% CI]**	SE_b	**β**	***p***	***F***	R^2_{adj}
Model 1				<.001	17.17	.44**
Age	-0.04 [-0.18, 0.11]	0.07	-.05			
Premorbid IQ	0.20** [0.14, 0.27]	0.03	.65**			
Gender	0.54 [-1.72, 2.80]	1.13	.05			
Model 2				<.001	14.34	.47**
Age	-0.03 [-0.17, 0.12]	0.07	-.04			
Premorbid IQ	0.18** [0.11, 0.25]	0.04	.58**			
Gender	0.17 [-2.07, 2.41]	1.12	.02			
Education	1.35 [-0.08, 0.25]	0.72	.20			
Model 3				<.001	11.47	.46**
Age	-0.02 [-0.16, 0.13]	0.07	-.02			
Premorbid IQ	.18** [0.10, 0.25]	0.04	.57**			
Gender	0.23 [-2.03, 2.49]	1.13	.02			
Education	1.18 [-0.34, 2.70]	0.76	.17			
Marital status	0.82* [-1.50, 3.14]	1.13	.08*			

Note. *p < .05, ** p < .001

Model 1 consisted of age, premorbid IQ and gender and explained 44%, R^2_{adj} = .44, p < .001, of the variance in global neurocognitive function performance. The only significant predictor was premorbid IQ, β = .653, p < .001. Age, β = -.05, p = .618, and gender, β = .05, p = .634, were not significant predictors.

The variance explained increased to 47%, ΔR^2 = .03, R^2_{adj} =.47, p < .001, when education was introduced in model 2. Premorbid IQ was the strongest predictor, β = .65, p < .001. However, age, β = -.04, p = .722; gender, β = .02, p = .880; and education, β = .20, p = .064, were not significant predictors.

In the final model the total variance explained was 46%, ΔR^2 = .00, R^2_{adj} = .46, p < .001, after marital status was added. The strongest significant predictor was premorbid IQ, β = .57, p < .001, and being unmarried had a weak prediction of increased GCF score, β = .08, p = .026. The not significant predictors were education, β = .17, p = .131; age, β = -.02, p = .261; and gender, β = .02, p = .154.

Group Differences in Cognitive Domains

An analysis of covariance (ANCOVA) was utilised to investigate group differences in neurocognitive performance in the six different domains and GCF controlled for the significant covariates: age, premorbid IQ, gender, education, and marital status. Boxplots were investigated to spot any possible outliers; however, none were found. Levene's test for homogeneity of variances were not significant for any of the ANCOVAs, with significant leveles varying between F(1,123) = 2.28, p = .133 and F(1,123) = 0.00, p = .950. The sample Levene's tests were from the ANCOVAs run on planning and visual memory, respectively. The results of the ANCOVA are summarised in Table 7.

There was a significant difference in GCF performance scores between the PWH and the PWoH, F(1, 123) = 15.83 , p < .001. A pairwise comparison post hoc test revealed that the PWH (M_{adj} = 39.97, SE = 0.54) had a lower performance mean than the PWoH (M_{adj} = 43.14, SE = 0.55), ΔM = -3.17, p < .001.

Additionally, there was a significant difference between the groups in scores for non-verbal learning, F(1, 123) = 14.68, p < .001. A pairwise comparison post hoc test revealed

that the PWH (M_{adj} = 40.50, SE = 1.06) had a significantly lower mean performance than the PWoH (M_{adj} = 46.48, SE = 1.07), ΔM = -5.98, p < .001.

Table 7

Neurocognitive Test Performance Means, Adjusted Means, Standard Deviations, and ANCOVA Results Summarised

	PWH			PWoH		
		Unadjusted	Adjusted[a]		Unadjusted	Adjusted[a]
Tests	***n***	***M (SD)***	***M (SE)***	***n***	***M (SD)***	***M (SE)***
Global cognitive function	63	39.17 (5.35)	39.97 (0.54)	62	43.95 (5.23)	43.14 (0.55)
Non-verbal learning	63	39.97 (9.55)	40.50 (1.06)	62	47.02 (8.87)	46.48 (1.07)
Planning	63	31.78 (6.53)	32.12 (0.91)	62	35.81 (7.60)	35.46 (0.91)
Visual memory	63	51.13 (8.13)	52.04 (1.04)	60	54.03 (9.96)	53.08 (1.07)
Divided attention	60	34.07 (7.64)	34.71 (0.89)	62	38.40 (6.81)	37.78 (0.87)
Spatial attention	61	38.04 (9.77)	39.38 (1.14)	62	45.09 (8.75)	43.77 (1.13)
Selective attention	62	40.39 (8.36)	41.28 (0.96)	62	43.75 (7.33)	42.86 (0.96)

Tests	***F***	***p***	η_p^2	***d***[b]	**1-β**[c]
Global cognitive function	15.83	<.001	.12	.92	.98
Non-verbal learning	14.68	<.001	.11	.78	.97
Planning	6.28	.014	.05	.60	.70
Visual memory	0.45	.504	.00	.36	.10
Divided attention	5.75	.018	.05	.62	.66
Spatial attention	7.02	.009	.06	.77	.75
Selective attention	1.26	.263	.01	.43	.20

Note. [a]Adjusted for the covariates: age, premorbid IQ, gender, education, and marital status.

[b]*d* = Cohen's *d*

[c]1- β = Observed power

Moreover, the two groups performed significantly different in the test for the planning domain, $F(1, 123) = 6.28$, $p = .014$. A pairwise comparison post hoc test revealed that the

PWH (M_{adj} = 32.12, *SE* = 0.91) were significantly worse at the planning test than the PWoH (M_{adj} = 35.46, *SE* = 0.91), ΔM = -3.34, p = .014.

PWH and PWoH were significantly different in their ability to split their attention, $F(1, 120) = 5.75$, p = .018. A pairwise comparison post hoc test revealed that the PWH (M_{adj} = 34.71, *SE* = 0.89) had a significantly lower mean performance than the PWoH (M_{adj} = 37.78, *SE* = 0.87), in the divided attention test, ΔM = -3.07, p = .018.

Furthermore, there was a significant difference in the spatial attention domain, $F(1, 121) = 7.02$, p = .009. A pairwise comparison post hoc test revealed that the PWH, M_{adj} = 39.38, *SE* = 1.14, had a significantly lower mean performance than the PWoH, M_{adj} = 43.77, *SE* = 1.13, ΔM = -4.38, p = .009.

Lastly, there were no significant group differences in neurocognitive function in neither the visual memory domain, $F(1, 121) = 0.45$, p = .504, nor selective attention domain, $F(1, 122) = 1.26$, p = .263. The observed power (1-β) for the ANCOVA for these test performances were .10 and .20, respectively.

Discussion

This study aimed to determine the prevalence of NCI in Iranian ART treated PLWH; to detect the sociodemographic and medical factors that predict neurocognitive function; and find significant group differences in neurocognitive function and the six cognitive domains tested. The results showed that there was a significant difference in the prevalence of NCIs between the PWH and PWoH based on the global neurocognitive function performance scores. The prevalence of NCIs in PWH in Iran, 59%, matched the higher end of international findings (Haddow et al., 2018; Heaton et al., 2010; Kato et al., 2020; Wright et al., 2008; Zenebe et al., 2023). It was a close match to NCI prevalence in India, which was

approximately 60% (Wright et al., 2008), and the U.S., which rested around 52% (Heaton et al., 2010). This study, however, did not operationalise NCIs based on the Frascati criteria, and thus cannot draw any conclusions of the severity of the NCIs in question.

Our findings on NCI prevalence for PWH in the specific cognitive domains do not entirely match the findings in Heaton et al. (1995). According to Heaton et al. (1995), the attention domain had the highest prevalence of impairment, whilst memory and executive function (found as abstraction in Heaton et al. (1995)) were in the mid to lower end of impairment percentage. However, in our study, NCI prevalence for PWH in the attention domain alternated between 33-44%, a considerable shift in percentage. Furthermore, prevalence in executive function in PWH in our study was at 79%, planting it firmly in the higher end of NCI prevalences. The prevalence of NCIs in PWH and PWoH based on their non-verbal learning test performance, which falls under the memory domain, was 81% and 46% respectively. Comparatively, the highest percentage of prevalence in Heaton et al. (1995) was 61%. The difference could be explained by different criterias for NCIs, where the results from Heaton et al. (1995) were based on the Frascati criteria and our NCIs were based on ROC curves cut offs.

Secondly, this study aimed to investigate what sociodemographical and medical characteristics predict NCIs. The analysis revealed three main characteristics for the PWH: gender, marital status and CD4+ T-cells/mm^3. Our findings support that there are some properties of the HIV infection, and sociodemographic and psychological characteristics of PWH, which predict neurocognitive functions. However, to investigate the direction of the relationship, one would have to perform an experimental study.

Our results indicated that identifying as a woman increased the risk of NCI in Iranian PWH, which is supported by prior findings (Robertson et al., 2014; Rubin et al., 2019). This relationship can be explained by women tending to have a higher prevalence of comorbid

symptoms, such as depression (Robertson et al., 2014), and other factors such as trauma and poverty which can contribute to low cognitive reserves (Maki et al., 2015). Depressive symptoms, although not significant in our study, have been associated with poorer neurocognitive function (Nanni et al., 2015). Interestingly, Maki et al. (2015) found that for women, HIV infection have small effect sizes on cognition, whilst other risk factors such as reading level and age were a stronger predictor of NCIs. This could indicate that women are at higher risk of developing NCIs, regardless of HIV serostatus. In our study, there was not a significant difference in NCI prevalence between women and men (p = .053). However, the gender distribution was not equal with men (N = 80) and women (N = 46), so this result should be taken with a grain of salt.

Additionally, women in Iran are at a hightened risk of getting infected by HIV without their knowledge. For instance, female sex workers in Iran have a 2.1% chance of catching an HIV infection (Nanni et al., 2015). Female sex workers in Iran are also heavily stigmatised and tend to avoid getting tested for HIV infection or other sexually transmitted diseases. A study by Shokoohi et al. (2016) reported numbers as low as only 27.5% of female sex workers had gotten tested and received results of their HIV test in the past year. As mentioned in the introduction, legacy effect describes the occurrence that untreated HIV infection can result in irreversible damage to neurocognitive function, even after the patients received ART (Alford & Vera, 2018). This speculated link between legacy effect and female sex workers with HIV has not been studied due to the stigmitisation and illegality of sex work. Furthermore, the stimgatisation of HIV can affect women who are not female sex workers but who have still contracted HIV through sexual intercourse. Approximately 76% of female PWH report their transmission as being caused by their sexual partners (Nanni et al., 2015). In our sample, 22 (76%) female PWH reported the cause of transaction as related to sexual activities. Women tend to avoid VCT centres in fear of being perceived as immodest, and modesty is upheld as a

virtue in Iranian culture (Shirpak et al., 2007). This, in addition to the previously mentioned risk factors such as depression and low cognitive reserves, indicates that female PWH are at a hightened risk of developing NCIs and thus future interventions should be aimed at Iranian women.

Being married predicted NCIs in PWH, whilst being unmarried predicted a slight increase in GCF in the PWoH. There is not much research on the relationship between marital status and HIV associated NCIs, but marital status has been linked to general mental and physical health in the U.S (Liu et al., 2019) and in particular in an ageing population (Feng et al., 2014; Hakansson et al., 2009). Being married, as opposed to being single, widowed or divorced-seperated, is linked to longer life expectancy and increased life quality. In particular, in a Chinese population, married men were significantly less likely to have cognitive dysfunction than unmarried men, while there was no effect for women (Feng et al., 2014). Interestingly, in Western studies, there were observed effects of marital status, but no gender differences (Hakansson et al., 2009; Liu et al., 2019). However, in an Iranian study, marital status did not significantly predict cognitive function among an elderly population (Aajami et al., 2020). All in all, the findings on marital status are mixed and underrepresented in research on cognitive function. Our mixed findings of being unmarried significantly predicting a decrease, for the PWH, and an increase, for the PWoH, in GCF scores fall within the mixed findings on this possible link. As our study identified it as a significant predictor, it could be interesting to allocate more research on this.

Higher counts of CD4+ T-cells/mm^3 also predicted higher GCF scores in PWH. CD4+ T-cells/mm^3 is associated with the severity of the HIV infection progression, as the HIV infection deplete the amount of healthy CD4+ T-cells in the central nervous system. This supports the conclusion that severity of HIV infection is negatively associated with GCF. The duration of HIV infection and duration of ART, interestingly, were not associated with GCF

or CD4+ T-cells/mm^3 in PWH. This could indicate that the ART treatment was effective at suppressing HIV RNA in the plasma, the treatments resulted in low CSF viral escape and/or was effective at replenishing the CD4+ T-cells, and that there were few legacy effects in our sample. This finding is not in accordance with studies that show long term ART negatively predicts GCF (Alford & Vera, 2018); however, other studies have found an improvement of NCIs (Maschke, 2000). The studies which found negative long-term effects hypothesise that the neurotoxicity of ART, the metabolistic side-effects of long term ART, or constant inflammation, could negatively affect neurocognitive function in PWH (Alford & Vera, 2018). Our results support the conclusion that ART treatment appears to reduce the risk of developing NCIs, given that the CD4+ T-cells/mm^3 function as a marker for the effectiveness of the ART drugs.

Our analyses did not support prior findings in support of the effect of education and premorbid IQ on neurocognitive performance in PWH. Levels of completed education was only a significant predictor for PWH when marital status was excluded from the model, and not at all for PWoH. Previous studies have found levels of education predicting neurocognitive function in PWH (Haddow et al., 2018; Zenebe et al., 2023). However, the support for education is mixed, as there are also several studies that have not identified levels of education as a significant preditcor (Zenebe et al., 2023). Unique to our study, as far as we are aware, our findings indicate that there are some properties of levels of education that explain the same variance as marital status in Iranian PWH. This possible link between levels of education and marital status could be interesting to devote more research to, and could perhaps in the future inform future interventions. Additionally, premorbid IQ was a weak predictor in the initial model, and was not significant as more predictors were added to the regression analysis for PWH. The same tendency was not found in PWoH, where premorbid IQ was the strongest predictor of neurocognitive function. Our findings indicate that there are

other sociodemographic and medical characteristics in PWH that explain variances in GCF, such as gender, education, marital status and CD4+ T-cell count/mm^3. To the best of our knowledge, most studies include premorbid IQ as a controlling variable without reporting the strength and direction of its effect on cognitive function in PWH, with the exception of a study which found that Cognitive Reserve Index, which is strongly associated with IQ, has a positive effect on cognitive functioning (Milanini et al., 2016). The effect of IQ on NCI prevalence in PWH is therefore relatively unknown.

Similar to levels of education and premorbid IQ, age was not a significant predictor of NCIs in Iranian PWH. Unlike our findings, age is generally identified as a strong predictor of NCIs in PWH (Ding et al., 2017), as it is hypothesised that HIV can lead to accelerated cognitive ageing in PWH (Grant, 2008). However, there are mixed findings on interaction effects between HIV and ageing (Alford & Vera, 2018). Nevertheless, ageing is often a predictor of neurocognitive performance. The lack of significant associations in our study could be attributed to the strict inclusion and exclusion criteria, where participants above the age of 50 were excluded from the final analyses. A study by Ding et al. (2017) found that there are significant main and interaction effects between age and NCIs in Chinese PWH. The study consisted of participants split into three age groups: 40-49, 50-59 and 60-82 years, and the results indicated that the significant differences was attributable to the performance of the oldest age group and youngest, and not the group aged 50-59 (Ding et al., 2017). In other words, there was a significant difference between PWH aged above 60 and below 50, because the youngest group did not experience accelarated cognitive ageing yet. Furthermore, the mean age of the Iranian PWH were 36.76, indicating a younger sample. Future research could investigate the association between cognitive ageing and HIV in an older sample of Iranian PWH.

Lastly, the study aimed to determine what domains of cognitive functioning there were group differences in. There were significant differences in neurocognitive performance scores between PWH and PWoH in all tests except for visual memory and selective attention. However, the observed power for the ANCOVAs of the two tests that were not significant was low, varying between $1-\beta = .10 - .20$, indicating that our analysis did not have enough power to detect a meaningful effect. It could prove useful, therefore, to conduct the study again with sufficient power before drawing any hard conclusions. The ANCOVAs for the other tests had sufficient observed power to detect substantial effects, and thus there appears to be some characteristic with PWH, aside from the covariates controlled for, that are involved with neurocognitive function in the memory domain, executive function, and attention domain.

Limitations and Future Directions

There were some limitations in our study. We were not able to assess the participants quality of sleep before the neurocognitive tests. Additionally, alcohol dependence was not included in the analysis, as alcohol is illegal in Iran and most participants would therefore not disclose this information. Future studies could make the appropriate adjustments to the study design to cover these limitations.

The strict exclusion criteria applied in the study reduced the total sample size. We implore future research to replicate our study with looser exclusion criteria to increase the sample size, and thus increase the statistical power, to investigate group differences in performance scores in visual memory and selective attention. Slacker exclusion criteria could also make it possible to further investigate the relationship between NCIs and ageing, as this current study did not allow for the possible cognitive ageing to have taken much effect.

Additionally, as this was an exploratory cross-sectional design we were not able to investigate any causal relationships. It would be interesting to explore the causal relationship between the risk factors found in this study and GCF, as this could inform future interventions.

Lastly, our study did not investigate the severity of the NCIs, therefore it could be informative to examine whether there are any differences in risk factors for milder and more severe forms of NCIs, as per the Frascati criteria.

Conclusion

In the present study the prevelance of NCIs in Iran was found to be 59% for the PWH and 19% for the PWoH. The NCI prevalence for PWH matches the higher end of international findings. It can be concluded that despite similar prevalence rates of NCI in Iran and the world, the NCI profile appears different among Iranian PWH in comparison to the American profile presented in (Heaton 1995). Furthermore, our findings indicated that there are some properties of Iranian PWH which put them at a higher risk of developing NCIs than PWoH. The risk factors identified for NCIs in PWH were identifying as a woman, being unmarried and lower CD4+ T-cells/mm^3. Although they were significant correlates, levels of education, premorbid IQ, and age did not significantly predict GCF scores in PWH. For PWoH, however, only premorbid IQ and being unmarried predicted increases in GCF, whilst all other correlates were not significant predictors. Performances in non-verbal learning and visual memory, both representing the memory domain, and planning, representing the excecutive function and abstraction domain, resulted in the highest prevalence of impairments in PWH in our study. In other words, the PWH performed particularly worse than PWoH on tests for memory and executive function. When controlled for confounding variables, there were no significant differences between PWH and PWoH in visual memory and selective attentnion. Interestingly, divided attention, spatial attention, and selective attention, all representing

cognitive function in the attention domain, were found to have the lowest NCI prevalence for both PWH and PWoH, meaning both groups performed well in the attention tests. Future studies could apply looser exclusion criteria, particularly including participants of older age, to investigate the effect of cognitive ageing on NCIs in Iranian PWH. For future interventions it would be necessary to investigate the causal relationship between the predictors and NCIs, as well as investigating predictors of milder and more severe degrees of NCIs.

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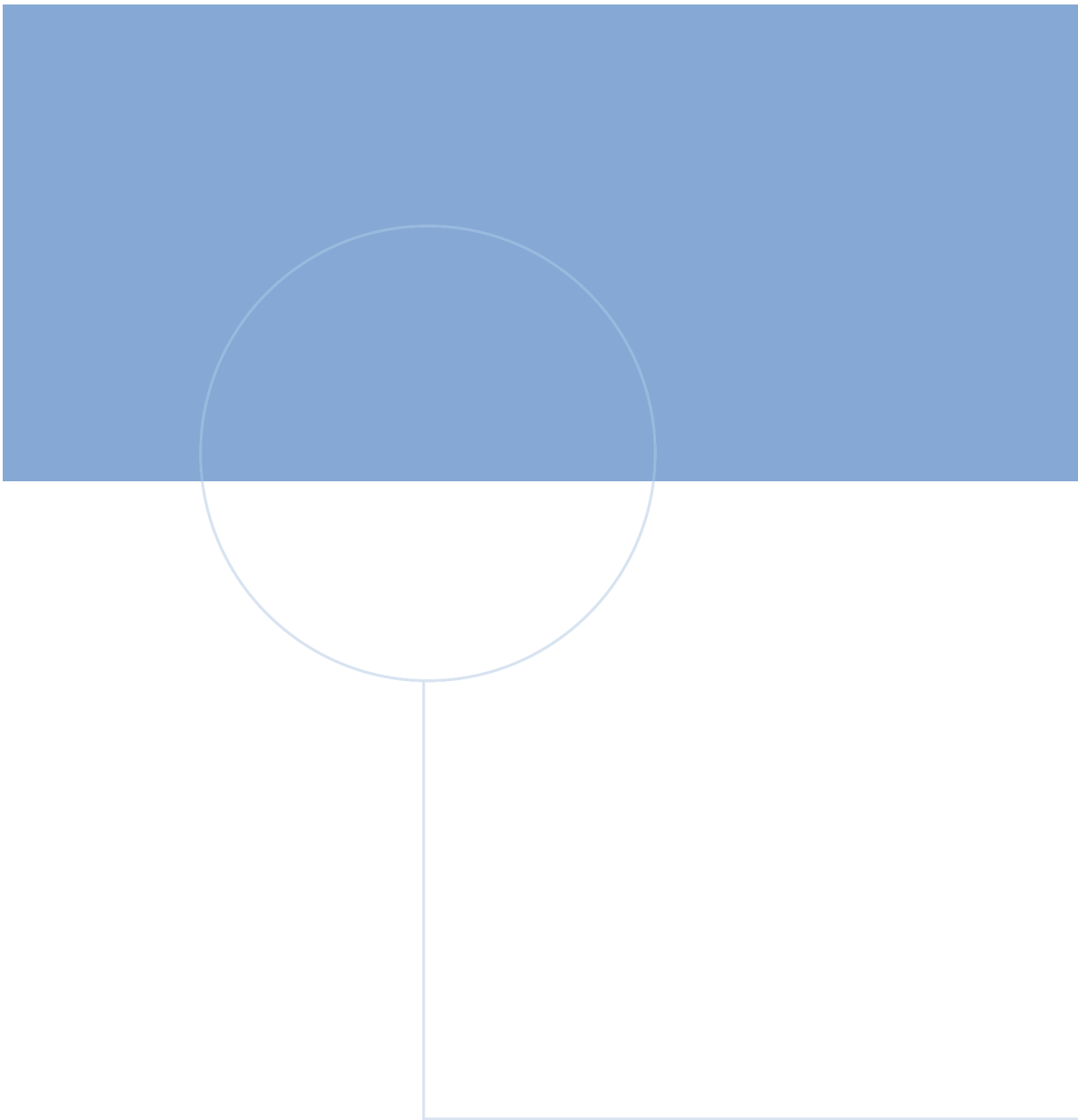

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