The Prevalence And Outcomes Of Depression In Older HIV-Positive Adults In Northern Tanzania: A Longitudinal Study

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Research Article

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ABSTRACT

Background: Studies of depression and its outcomes in older people living with HIV (PLWH) are currently lacking in sub-Saharan Africa

Objectives: To investigate prevalence of psychiatric disorders in PLWH aged ≥50 years in Tanzania focussing on prevalence and two-year outcomes of depression.

Method: PLWH aged ≥50 were systematically recruited from an outpatient clinic and assessed using the Mini-International Neuropsychiatric interview (MINI). Neurological and functional impairment were assessed at year two follow-up.

Results: At baseline, 253 PLWH were recruited (72.3% female, median age 57, 95.5% on cART). DSM-IV depression was highly prevalent (20.9%), whereas other DSM-IV psychiatric disorders were uncommon. At follow-up (n=162) DSM-IV depression non-significantly decreased (14.2% -11.1%) χ^2:2.48 p=0.29). Baseline depression, was associated with increased functional (p=0.018), and neurological impairment (p<0.001) and negative life events (p=0.001) at follow-up, but HIV and sociodemographic factors were not.

Conclusions: In this setting, depression appears highly prevalent and associated with poorer outcomes. This may be a future intervention target.

Keywords HIV-associated neurocognitive disorders, sub-Saharan Africa, depression, Tanzania, older adults

Resumen

Antecedentes: Actualmente faltan estudios sobre la depresión y sus resultados en personas mayores que viven con el VIH en el África subsahariana

Objetivos: Investigar la prevalencia de trastornos psiquiátricos en personas que viven con el VIH mayores de 50 años en Tanzania centrándose en la prevalencia de la depresión y los resultados longitudinales después de dos años de seguimiento

Método: Personas viviendo con el VIH mayores de 50 años fueron sistemáticamente reclutadas y evaluadas mediante la Mini-Entrevista Neuropsiquiátrica Internacional

(MINI). El deterioro neurológico y funcional se evaluó en el segundo año de seguimiento.

Resultados: Se reclutaron 253 participantes (72,3% mujeres, mediana de edad de 57 años, 95,5% en cART). La depresión del DSM-IV fue altamente prevalente (20,9%), mientras que otros trastornos psiquiátricos del DSM-IV fueron poco frecuentes. En el seguimiento (n=162) la depresión del DSM-IV disminuyó no significativamente (14,2% -11,1%) χ2:2,48 p=0,29). La depresión se asoció con deterioro funcional (p = 0,018), deterioro neurológico (p<0.001)
y eventos vitales negativos (p=0,001) en el seguimiento, pero el VIH y los factores sociodemográficos no fueron associados.

Conclusiones: En este contexto, la depresión parece altamente prevalente y se asocia con peores resultados. Este puede ser un objetivo de intervenciones en el futuro

INTRODUCTION

There are over 38 million people living with HIV (PLWH) worldwide(1). New infections total 1.7 million annually, two thirds of which occur in Sub-Saharan Africa (SSA)(1). Rapidly expanding access to combined antiretroviral therapy (cART) has markedly increased life expectancy of PLWH. In Africa, the population aged ≥50 is expected to triple by 2030 from 74.4million to 235.1million(2). SSA currently accounts of 60% of all PLWH over the age of 50(2). This newly emergent ageing population brings new challenges in the form of chronic HIV-associated comorbidities.

Mental disorders (primarily depression) are predicted to become the leading cause of disability worldwide by 2030, with over 322 million people currently affected(3, 4). Rates of depression in HIV are reportedly 2-4 times higher than the general population(5). In SSA, estimated pooled prevalence of 9-32% is reported in PLWH(5). Depression is well-recognised to negatively impact HIV-disease outcomes e.g. CD4 count or viral load (in SSA and elsewhere) resulting in treatment failure, higher HIV viral load and increased mortality(6).

The pathophysiology of depression in HIV is not well understood. Current hypothesised aetiologies include biological and psychosocial pathways(7). The biological pathway attributes depression to persistent viral presence in the central nervous system (CNS) thus acting as a reservoir(7). This prolongs immunological activation and releases toxic viral proteins and inflammatory cytokines which results in depression as part of a spectrum of neurological impairment due to the resultant neuronal damage(7). The psychosocial pathway attributes depression to the psychological burden of living with a chronic, disabling and stigmatised disease(7).

Depression and HIV may also have a bidirectional relationship in that depression appears to be both a risk factor for, and consequence of, HIV infection(6). An additional challenge is that depression may be associated with individual cART medications (e.g. Efavirenz) and with common comorbidities (particularly tuberculosis (TB))(8, 9)..

Despite the newly ageing HIV population, few studies have investigated depression in older PLWH. These studies, appraised in the discussion, mostly use cross-sectional data and longitudinal data are lacking. In addition, existing SSA studies of depression in HIV focus almost exclusively on younger populations and/or specific higher risk groups, such as intravenous drug users, marginalised groups and untreated populations(10, 11). Current data, therefore, lack applicability to the cART-treated ageing population rapidly increasing in SSA.

Older PLWH may be at specific increased risk of neurological impairment and disability. For example, HIV-associated neurocognitive disorders (HAND) affect up to 50% of older PLWH worldwide(12). Since depression is a well-recognised risk for and consequence of, neurodegenerative dementias(13), data on neurocognitive outcome of depression in older PLWH is needed and currently lacking.

In summary, depression and HIV are predicted to become the first and second leading causes of disability worldwide by 2030 resulting in huge potential individual and societal consequences for those affected(3, 14) . There is a critical gap in current knowledge regarding depression in older PLWH, potentially modifiable aetiological factors and outcomes. Without assessment of the longer-term effect of

depression, progress in low-resource settings may not be prioritised due to lack of evidence to inform policy makers.

We therefore aimed to:

1. Estimate prevalence and risk factors of depression, in the context of other psychiatric disorders, in older PLWH in Tanzania,
2. Estimate longitudinal prevalence of depression and its neurological and functional outcomes in PLWH aged ≥50 years receiving standard HIV-clinic follow-up and
3. Explore the relationship of depression to the biological and psychological hypothesised aetiological pathways.

METHODS

Setting

The study took place at Mawenzi Regional Referral Hospital (MRRH) HIV Care and Treatment Centre (CTC) in the Kilimanjaro region of Northern Tanzania. This clinic is a government-run, free of charge service. Estimated national prevalence of HIV infection in Tanzania is 4.6% with 71% of those aware of their HIV status receiving treatment (UNAIDS, 2018). At baseline (2016) 820 PLWH aged ≥50 years were registered with the MRRH clinic. MRRH has a psychiatric clinic, though a trained psychiatrist (responsible for the entire Kilimanjaro region) was recruited only in 2018. Currently, Tanzania has only 0.52 qualified mental health workers per 100,000 population(15).

Ethics

Ethical approval was granted by the Tanzanian National Institute of Medical Research and Kilimanjaro Christian Medical College Research Ethics Committee (No. 896). Verbal and written information was given to each participant before informed consent was obtained. If participants lacked capacity to consent, assent was sought from a close relative. Consent was rechecked at follow up. The study protocol included locally agreed referral pathways for individuals diagnosed with significant psychiatric disorders.

Recruitment, sampling and background data

The primary purpose of the baseline study was identification and screening of HIV-associated neurocognitive disorders (HAND) and a detailed description of recruitment and baseline assessment has previously been published(16). In brief, a systematic sample (every third eligible individual) was recruited March-May 2016. Inclusion criteria were individuals aged ≥50 years attending routine follow-up. Those attending emergency appointments, too physically unwell to comfortably participate or newly diagnosed were excluded.

Individuals included at baseline were offered follow-up when attending routine appointments annually during the study follow-up period and included in longitudinal analysis if evaluated between March-May 2018. Detailed HIV-disease severity, e.g. CD4 count or viral load, and comorbidity data were obtained from standardised clinic records as previously reported(16). Other demographic data were self-reported and corroborated by informants where necessary.

Assessment of Psychiatric Disorders

Baseline screening and diagnosis of depression and other psychiatric disorders were completed by a doctorate-level specialist nurse and specialist nurse with experience of older person's mental health research (JR, AK). A local translation of the 15-item Geriatric Depression Scale (GDS) was used to screen for depression, having previously been used for epidemiological studies in SSA(17, 18). A cut-off of 5/15 (previously used for ICD-10/DSM-IV depression in SSA) was applied. The GDS was interviewer-administered, an accepted method in low-literacy settings(19).
Psychiatric disorders were identified using a local translation of the Mini International Neuropsychiatric Interview (MINI), a widely used structured 'stem and leaf' tool which utilises the DSM-IV criteria and is validated for depression screening in PLWH in SSA(20).

Neurological Impairment

Neurological symptoms were self-reported by structured questionnaire (**supplementary table I**) and included memory, thinking, balance impairment, subjective slowness and loss of feeling in the hands/feet.
HIV-associated neurocognitive disorders (HAND) by AAN (2007) criteria were classified by consensus panel (SM-P, EML, RA, TL). Full HAND assessment (details previously published(21)) included locally normed low-literacy neuropsychological test battery, structured mental state examination, abbreviated neurological examination and creation of summary case notes for consensus panel review.

Functional Impairment

Subjective functional impairments (employment/home responsibilities) were self-reported (**supplementary table I**). Informant collateral history to confirm/refute cognitive or functional impairment was obtained, usually from a close relative (by

telephone where necessary), with participants' consent. Informants were told this was a general ageing study and HIV was not mentioned in order to protect patients' confidentiality. Overall clinician-rating of function was recorded using the Karnofsky performance scale (0-100%)(22) widely used in HIV settings. This rating considered self-reported impairment, clinical assessment and collateral history.

Follow-up assessment

Follow-up assessment (2018) was similar to baseline, with the following changes. 1: All individuals were screened with the GDS-15 and, only if screen positive (≥5/15), the DSM-IV depression element of the MINI completed (AK). Other DSM-IV psychiatric disorders were not evaluated due to very low prevalence of disorders other than depression at baseline and to avoid participant fatigue. 2: Follow-up participants were asked if they had experienced any significant negative life events in the previous 2 years (and if necessary, prompted, e.g., bereavement, significant loss or other negative life events). 3: HIV viral load measurement became locally available in 2017 (following a change in national guidelines) and was included as a HIV-disease severity outcome at follow-up. Viral suppression was defined as ≤20 copies/ml.

Statistical Analysis

Data analysis was supported by IBM SPSS (version 26; IBM, Armonk, NY, USA). Standard descriptive statistics (e.g., mean, median, standard deviation (SD), interquartile range (IQR) and frequency) and inferential tests (e.g., chi-squared, Mann-Whitney U and t-test) used for group comparisons depending on the level and distribution of the data. All data analyses were two-tailed at a 5% significance level.

Only those with full data at both time points were included in longitudinal analysis (253 and 162 participants in 2016 and 2018 respectively).

RESULTS

Of 253 individuals with complete data at baseline 2016, 162 (64.0%) were followed up in 2018 (**figure 1**). Those followed-up did not significantly differ in demographic (% female, median age, % primary educated) or HIV-disease severity factors (mean CD4, WHO stage 1/2 vs 3/4) from those not followed-up (**figure 1**). Demographic, HIV-disease and comorbidity characteristics at baseline are summarised in **supplementary table II** and are also previously published(16, 21). The majority were female (72.3%), educational level was low (64% completed primary education), current HIV-disease control was good (95.5% cART-treated, mean CD4 526.5 mm/l), though most (60%) had advanced disease (WHO stage 3 or 4).

Depression and other psychiatric disorders at baseline (2016)

Affective and non-affective psychiatric disorders by DSM-IV MINI criteria are listed in **table I.** Depression was highly prevalent by both GDS-15 (53, 20.9%) and MINI DSM-IV criteria (42, 16.6%) (table I). Few were treated with psychiatric medication (DSM-IV n=2 (3.8%), GDS-15 n=3 (7.1%) prescribed amitriptyline, usually low-dose). Other psychiatric disorders (anxiety disorders, psychotic disorders) were uncommon. Alcohol dependence was reported by one participant and no participants reported other substance misuse.

DSM-IV depression at baseline was not associated with HIV-disease severity markers including legacy effect (proxy measure: nadir CD4), current efavirenz

prescription or TB treatment, measured sociodemographic factors, or presence of neurocognitive or functional impairments **(table II**).

Neurological and functional impairments

Neurological and functional impairments were common (**table I**) particularly neuropathy, headaches and difficulties with home and work tasks. Almost half (47.0%) met AAN HAND criteria.

Follow-up cohort 2016 -2018

A total of 162 individuals were fully assessed at baseline and follow-up.

Demographic and HIV-disease data at each time point are summarised in **supplementary data table III**. Between baseline and follow-up, GDS-15 depression significantly decreased (20.9% to 13.0% χ^2: 4.30 p=0.038) but there was a non-significant decrease of depression by DSM-IV criteria (16.6% to 11.1% χ^2:2.41 p=0.12).

Two-year outcome of depression at baseline

Outcomes of those with and without DSM-IV and GDS-15 depression at baseline are outlined in **table III and supplementary data table IV** respectively. Most HIV disease outcomes (CD4, viral suppression, WHO stage, medication adherence) were not significantly different in those with and without depression at baseline. The use of efavirenz significantly decreased (supplementary table III, 53.0% to 31.5% χ^2:91.30 p<0.001) and those on second line cART treatment increased.

Psychosocial outcomes

Individuals meeting DSM-IV or GDS-15 depression criteria in 2016 were significantly more likely to report negative life events in the previous year at follow up in 2018 compared to those who did not to meet depression criteria at baseline in 2016 (**table III, supplementary data table IV**). Unemployment at follow-up was associated with baseline depressive symptoms by the GDS-15 **(supplementary table IV)** but not DSM-IV criteria **(table III).**

Neurological outcomes

Self-reported neurological outcomes and functional impairment are illustrated in **figures 2 and 3**. Figure 2 shows those depressed at baseline had poorer neurological outcomes at follow up compared to those not depressed at baseline. While figure 3 shows those depressed by both MINI DSM-IV and GDS-15 criteria have poorer functionality by the Karnofsky performance status compared to non-depressed participants. Baseline DSM-IV depression was significantly associated with self-reported neurological impairment (impaired concentration, balance, slow hand movements) at follow-up but not a formal HAND diagnosis (**table III**).

Functional Impairment

At follow-up, self-reported difficulties with everyday tasks were twice as likely, and with home responsibilities three times as likely, in those with depression at baseline (figure 2, table III). Similarly, over 20% of those with depression at baseline were clinician-rated as substantially functionally impaired (Karnofsky ≤70%, indicating need for assistance with daily living activities) compared with ≤5% of those without baseline depression (**figure 3**). Prevalence of both HAND and functional impairment

increased by 12.3% and 5.1% respectively 2016 - 2018 though self-reported neurological symptoms decreased by 7.3%.

DISCUSSION

This study is the first to report prevalence of depression in older PLWH in SSA alongside biological, psychosocial and functional outcomes. We report a high depression prevalence (20.9% DSM-IV, 16.6% GDS-15), but were unable to identify other SSA studies using comparable diagnostic criteria.

One South African study (n=422) reported prevalence of 14.8% by ICD-10 criteria in a demographically similar rural cohort (median age 60 vs 57, % primary educated 52.4 vs 64.0) but with substantially lower cART treatment rates (95.5% vs 49.3%)(21). ICD-10 includes more somatic symptoms than DSM-IV, potentially resulting in overreporting in chronic disease(19).

Other high-income (USA)(23, 24) and middle-income settings (Brazil)(25) report prevalence of 39.1% (CES-D), 14.0% (DSM-IV) and 34.6% (GDS) respectively. These are socio-demographically different to this Tanzanian cohort (USA median age 54-55.8, %female 28-28.9, completed high school 78.7-82%)(23, 24) (Brazil mean age 57.6, %female 44.2, %literate 76.9, cART-treated 94.2%)(25)

These studies, like ours, report a high depression prevalence, (highest in higher-income settings) despite differing population demographics and proportion receiving cART. This is surprising as we might expect a higher depression prevalence in those cART-untreated given the biological inflammatory pathway hypothesis(26).

Baseline depression was not associated with any of the HIV-disease severity variables we investigated. Other cross-sectional studies frequently report worse HIV-disease outcomes and cART adherence. An East African study (Tanzania, Kenya and Uganda n=2307, 58.3 %female, median age 34-48) reported that depression was associated with 50% lower cART adherence and increased HIV viral load(27). This older cohort may be unusual given that almost all received cART (vs 68% in the East African study), and self-reported adherence was high(27). We may be observing a 'healthy survivor' effect which may to some extent be present in other older PLWH cohorts.

Prevalence of Other Psychiatric Disorders

There are few studies reporting prevalence of non-mood psychiatric disorders in HIV, particularly in LMICs, and we were unable to identify other studies of psychiatric disorders in older PLWH in SSA. Comparisons with other studies are therefore challenging.

Our reported rates of psychiatric disorders other than depression were low. Similar findings are reported at population level in the Global Burden of Disease survey (anxiety disorders 3.4% alcohol disorders 1.4% (28). SSA studies of younger PLWH report higher levels of both anxiety and alcohol disorders. A South African study (n=65, md age 30) reported a MINI DSM-IV generalised anxiety disorder prevalence of 6.7% and 10.1% alcohol dependence(29), whereas 21.7% met anxiety disorder criteria in a larger Nigerian study (n=300, median age 37)(30).

Though our cohort included individuals in 'middle age', the skew towards older age may be relevant. Anxiety disorders peak in middle age and decrease in older

age(31). Similarly, alcohol misuse peaks at age 25-34 in South African general population data(32).

Social circumstances may also be important. Much of our cohort were employed (88.5%) and lived with others (83%) compared to the younger South African cohort where a third lacked family support and unemployment rates were high (24.7%)(30).

The prevalence of mental disorders tends to be higher in those with chronic disease such as obesity, diabetes, heart disease, cancer and COPD and increases with the number of chronic diseases(28, 33). A meta-analysis investigating mental disorders in chronic disease reported a 36.6% prevalence of anxiety and/or depression in chronic disease, compared to 4.4% in the general population, and that chronic disease increased the risk of anxiety and/or depression by 310% using DSM-V and ICD-10 criteria(34). The population prevalence of comorbid mental disorders (depression, anxiety, bipolar disorders, schizophrenia) with chronic diseases is estimated at 45.8% in SSA(28, 33). It is surprising therefore that this older cohort with a chronic disease appear to have lower levels of both depression and other mental disorders(34).

Outcomes of Depression at Baseline

This is the only study we are aware of which investigates longitudinal outcomes of depression in older adults with HIV in SSA. The prevalence of depression appeared to decrease between baseline and follow up though this was only significant by GDS and not DSM-IV criteria. Longitudinal reductions in depression have been reported in other studies of PLWH (**supplementary table V**) though these are largely majority male populations in high income countries and/or intravenous drug user (IVDU)

settings. One SSA study reported 8.9% reduction over 6 months, in the context of young PLWH before and after commencing cART(29). Existing data are difficult to compare to our majority female cohort of older people stable on cART.

Persistent Depression and chronic inflammation hypothesis

Individuals depressed at baseline were more likely to 'screen-positive' on the GDS (depressive symptoms) but not to meet case-level DSM-IV criteria at follow-up. Depression is an episodic disorder and might be expected to remit over the two-year follow-up. However, a depressive episode increases the subsequent likelihood of another, in part due to the 'kindling' hypothesis where the level of stressor resulting in depression reduces over time (35-37) It is unclear whether these GDS findings represent subthreshold depression.

Chronic 'sub-threshold' depressive symptoms are seen in other chronic inflammatory diseases and also in conditions resulting in damage to frontal pathways (as in cerebrovascular disease) commonly reported to occur in chronic HIV infection(38). Increased CNS and peripheral inflammatory biomarkers are reported in depression and may reduce with antidepressant medication treatment(39).

HIV Disease Severity

We had hypothesised that depression could be associated with ongoing HIV-related inflammation in this cohort. However, baseline depression was not significantly associated with HIV-disease severity including viral suppression at follow-up. In contrast, other cross-sectional SSA studies report associations with poor medication adherence, high HIV viral load and low CD4 count(40, 41). This again may partly reflect the 'healthy survivor' effect and good HIV management seen in this cohort

where cART adherence and HIV-disease outcomes improved 2016-2018. The introduction of HIV viral load testing in 2017 may have contributed to this finding. The proportion receiving second line therapy (indicating treatment failure) increased, and cART adherence also improved, potentially due to improved disease monitoring and clinician feedback.

Lack of association with HIV-viral load does not exclude ongoing chronic inflammation and we noted an increased proportion receiving second-line therapy at follow-up. Chronic inflammation resulting from HIV infection may lead to depression (as for other chronic inflammatory conditions) despite a peripherally suppressed HIV viral load given that the CNS is a 'reservoir site' for the HIV virus, due to limited CNS cART penetration(42). This potential ongoing CNS inflammation and damage might explain the association of depression with poorer neurological outcomes but not the measured HIV-disease outcomes.

Neurological Impairment

Baseline depression was significantly associated with self- reported neurological and functional impairments at follow-up. It is unclear whether this represents a true increase.

Somatic manifestations of depression are common in older people and in SSA(43, 44). Limited access to mental health services in SSA may result in misdiagnosis of depression as physical illness(44). Self-reported 'slow hand movements' could represent residual depression symptoms (psychomotor retardation, anergia), somatic representations of distress or neurological impairment.

Similarly, ‘negative cognitions’ are well recognised in depression and may persist despite remission. It is possible therefore that individuals with depression over-reported symptoms and impairment.

Though self-reported neurological symptoms were associated with depression, the (potentially more objective) clinical diagnosis of HAND was not. In PLWH, depressive symptoms, but not objective neuropsychological performance, may explain the variance between self-reported and clinical findings(45). Furthermore, self-reported functional impairment may be inaccurate in those with cognitive impairment(46). However, neurological and functional impairments were not associated with depression at baseline, and other psychiatric diagnoses were uncommon, suggesting ‘over-reporting’ to be less likely. The significant associations reported at follow-up were self-reported and clinician-rated and included the objective measure of employment. This suggests that negative cognitive biases associated with depression are not the major explanation for our findings.

Psychosocial factors

Given that we found no association between depression and HIV-disease factors, psychosocial factors may be relevant. Multiple factors such as isolation, discrimination, stigma and living with chronic disease have been linked to depression in HIV(7). At baseline, we found no association between living alone, unemployment, educational background and depression, but depression symptoms (GDS-15 ≥5) were associated with unemployment at follow-up.

Self-reported significant negative life events at follow-up were more likely in those depressed at baseline though overall depression prevalence reduced. Significant life

stress is well-recognised to predict depression(7). Our findings suggest a possible bidirectional relationship. As discussed for neurological impairment, events may have been viewed more negatively due to negative cognitive biases(47).

HIV is well-recognised to negatively impact long term social and economic outcomes for families(48). Kenyan and South African data suggest earnings are lower in PLWH and that reduced earning potential results in sale of valuable assets such as livestock causing ongoing health and economic vulnerability(48). PLWH with depression may also be more likely to experience disability and reduced work productivity. In India, depression in HIV was associated with poorer environmental and social quality of life indicators (unemployment, low-income, poor diet, inadequate housing and lack of life partner)(49). Similarly, a Ugandan study reported PLWH with depression (PHQ-9 and MINI) to be more likely to be unemployed and/or have lower weekly income than those without depression(47). Therefore, depressed PLWH may be at higher risk of negative socioeconomic life events(50).

Individuals with depression may be more likely to experience difficult social situations, negative interactions and selectively focus on negative emotional stimuli(51). This may result in fewer intimate relationships, greater negative responses from others and greater emotional distress in response to social stressors(51). Consequently, PLWH with depression may be more likely to experience stressful life events and also respond more negatively to them, creating a double burden of disability, whilst having lower ‘reserve’ due to lower socioeconomic status(52). Conversely other studies report lower subsequent negative life events and stressors at follow-up in those with depression(29).

In summary, though comparable longitudinal data are lacking, it seems plausible that both HIV and depression may interact to result in greater self-reported negative life events and worse functional outcomes ('objective' and self-reported).

Limitations

We selected the GDS-15 given that this tool has previously been used in SSA but recognise that it was developed in high-income settings, and cultural differences in expressions of depression and distress are well-recognised. Though we used a local translation, this instrument may have some cultural limitations(53). Similarly, we used a local translation of the MINI, previously used in studies conducted in the same clinic(54), however, the low prevalence of some psychiatric disorders could be attributable to differences in cultural understanding. Though we report on some psychosocial outcomes, we did not obtain information on self-perceived stigma and socioeconomic background, risk and outcome factors which may have been relevant.

At baseline, psychiatric screening was completed by registered Tanzanian nurses with mental health research experience (one at doctoral level). Despite efforts to develop rapport, the sensitivity of the questions and well-recognised stigma associated with mental illness may have led to under-reporting of psychiatric symptoms. Due to scarcity of specialist mental health services in Tanzania, previous psychiatric disorders are likely to be undiagnosed and subsequently under-reported. Similarly, since depression is episodic, depression which was not present during the study period will have been missed.

In 2018, the psychiatric interview was abbreviated to prevent participant fatigue and retain as many participants as possible. In addition, there were low rates of other psychiatric disorders, therefore, we decided to focus on the highly prevalent depression disorder. This change may have impacted longitudinal findings. Self-reported negative life events may have been over or under-reported depending upon rapport established.

Neurological symptoms were self-reported. A neurological examination was completed at baseline and follow-up but was insufficiently comprehensive to fully corroborate symptoms reported (e.g., peripheral neuropathy). The lack of HIV viral load testing at baseline limited assessment of HIV-disease severity.

We had a relatively high rate of loss to follow-up. However, we were able to verify from clinic records that almost all not evaluated (72/91) remained under active HIV clinic follow-up and only 8/91 were recorded to have died. Though those seen and not seen at follow-up did not differ in recorded sociodemographic factors, it is not clear whether the follow-up cohort were representative in terms of outcome. We have no information on cause of death.

Study data collection corresponded with the crop-planting (rainy) season. Those failing to attend clinic at this time may have been fitter and more likely to be engaged in this employment, or conversely, less able to travel in difficult road conditions.

Conclusion

HIV is becoming a chronic disease and consequently, the burden on PLWH aged ≥50 is growing. This is the first longitudinal study of prevalence and outcomes of depression in older PLWH in SSA. Despite well controlled disease, significant

associations were found with neurological and functional impairment and an increased risk of subsequent negative significant life events. This suggests that depression may have long-lasting effects despite remission. This cohort, demographically typical of PLWH in Tanzania, markedly differs from high-income studies of older PLWH. There are likely to be differing aetiologies and risk factors for depression that are not currently understood. Further research should replicate these findings in SSA; identify those at greatest risk and determine whether interventions can reduce these observed negative outcomes.

FIGURES

Figure 1:

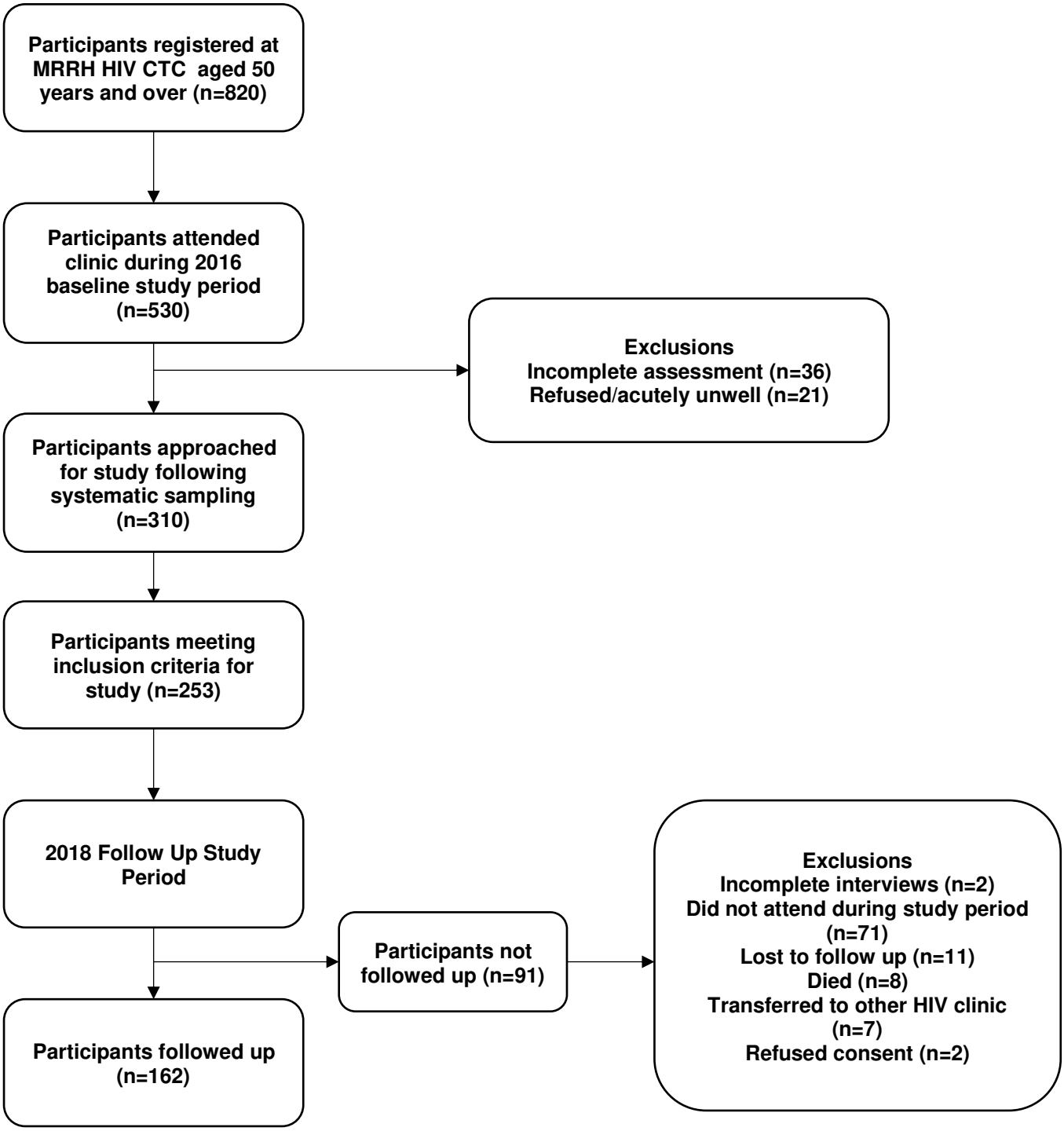


Figure 2:

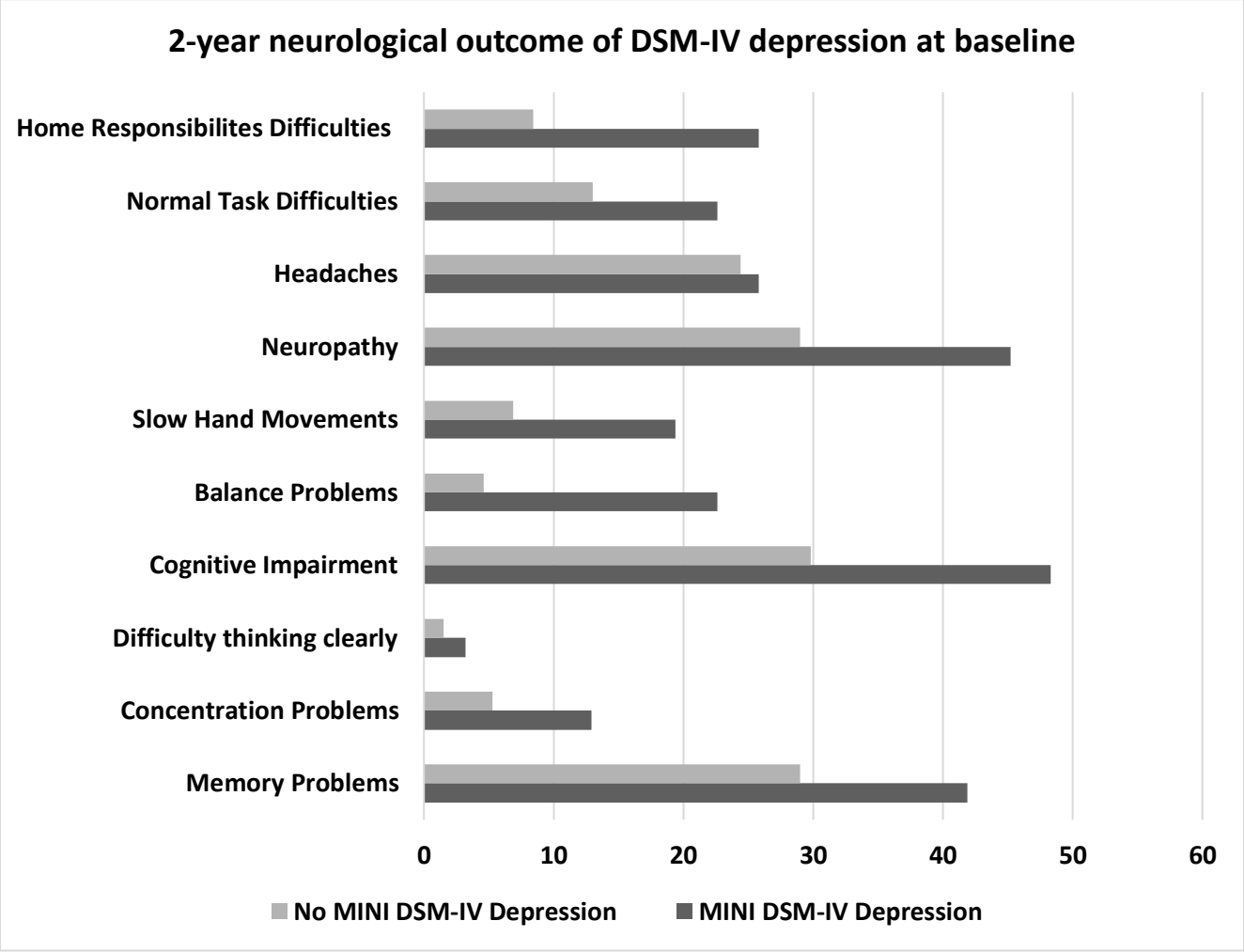
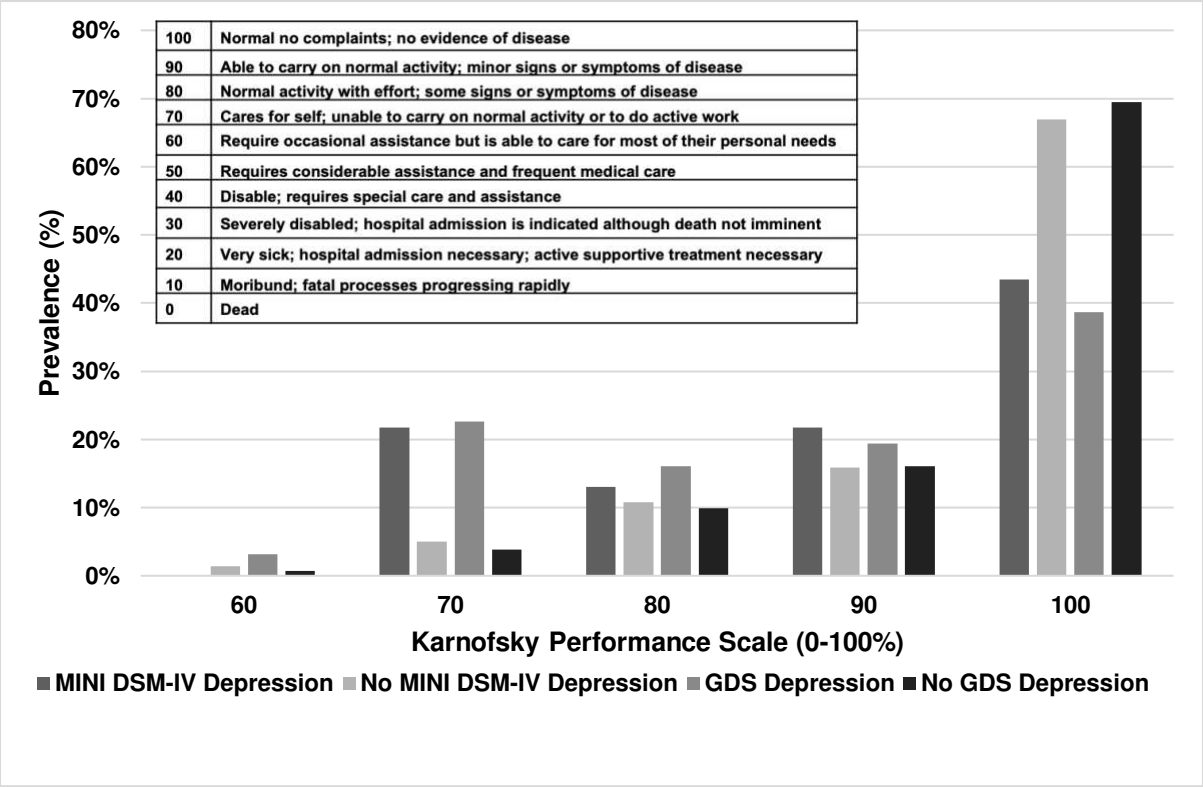

2-year neurological outcome of DSM-IV depression at baseline
Home Responsibilites Difficulties
Normal Task Difficulties
Headaches
Neuropathy
Slow Hand Movements
Balance Problems
Cognitive Impairment
Difficulty thinking clearly
Concentration Problems
Memory Problems
0
10
20
30
40
50
60
No MINI DSM-IV Depression
MINI DSM-IV Depression

Figure 3:


80%
70%
60%
50%
40%
30%
20%
10%
0%
Prevalence (%)
100 Normal no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some signs or symptoms of disease
70 Cares for self; unable to carry on normal activity or to do active work
60 Require occasional assistance but is able to care for most of their personal needs
50 Requires considerable assistance and frequent medical care
40 Disable; requires special care and assistance
30 Severely disabled; hospital admission is indicated although death not imminent
20 Very sick; hospital admission necessary; active supportive treatment necessary
10 Moribund; fatal processes progressing rapidly
0 Dead
60
70
80
90
100
Karnofsky Performance Scale (0-100%)
MINI DSM-IV Depression
No MINI DSM-IV Depression
GDS Depression
No GDS Depression

CAPTIONS FOR FIGURES

Figure 1: Study Flowchart. Those followed-up in 2018 did not significantly differ in demographic (%female 70.4 95%CI, χ^2:0.87 p=0.35, median age 59 95%CI, t-test:0.16 p=0.75, %primary educated 67.9 95%CI, χ^2:6.64 p=0.25) or HIV-disease severity factors (Mean CD4 530.2 95%CI, t-test:1.47 p=0.39, WHO stage 1/2 14.8%, WHO Stage 3/4 93.2%) from those not followed-up.

Figure 2: 2-year neurological outcome of MINI DSM-IV depression at baseline (2016)

Figure 3: Functional outcome by Karnofsky performance status in those with and without DSM-IV depression and/or depression symptoms GDS ≥5/15 at baseline

Table I : Prevalence of DSM-IV psychiatric disorders and self-reported neurological impairment in the baseline cohort (n=253)

Psychiatric Disorder		
	Prevalence (n, %)	**95% confidence interval**
Major Depressive Disorder	24 (9.5%)	5.9 – 13.1
Dysthymia/depression (missing = 3)	42 (16.6%)	12.4 – 21.6
Mania	3 (1.2%)	-0.1 – 2.5
Hypomania (missing = 2)	0	0
Panic Disorder (missing = 30)	2 (0.8%)	-0.3 – 1.9
Agoraphobia + panic (missing = 1)	0	0
Agoraphobia + no panic (missing = 29)	1 (0.4%)	-0.4 – 1.2
Social Phobia (missing = 1)	6 (2.4%)	0.5 – 4.3
Obsessive Compulsive Disorder	1 (0.4%)	-0.4 – 1.2
Post-Traumatic Stress Disorder	2 (0.8%)	-0.3 – 1.9
Alcohol Dependence	1 (0.4%)	-0.4 – 1.2
Substance Abuse	0	0
Mood Disorder/Psychotic Features (missing = 1)	4 (1.6%)	0.0 – 3.1
Any Psychotic Illness (missing = 1)	1 (0.4%)	-0.4 – 1.2
Generalised Anxiety Disorder (missing = 1)	3 (1.2%)	-0.1 – 2.5
Antisocial Personality Disorder (missing = 1)	0	0
Summary of Psychiatric Disorders		
Any Mood Disorder	46 (18.2%)	13.4 – 22.9
Any Anxiety Disorder	10 (4.0%)	1.6 – 6.4
Any Psychotic Disorder	7 (2.8%)	0.7 – 4.8
Any Alcohol Disorder	0	0
Psychiatric Medications (amitriptyline)	7 (2.8%)	0.75 – 4.79
Self-Reported Neurological Impairment		

Balance Issues (missing = 7)	30 (11.9%)	7.9 - 15.8
Slow Hand Movements (missing = 8)	27 (10.7%)	6.9 - 14.5
Neuropathy (missing = 8)	90 (35.6%)	29.7 - 41.5
Headaches (missing = 7)	90 (35.6%)	29.7 - 41.5
Normal Task Difficulties (missing = 10)	66 (26.1%)	20.7 - 31.5
Home Responsibilities Difficulties (missing = 10)	17 (6.7%)	3.6 – 9.8
Summary of Self-Reported Neurological Impairment		
Functional Impairment (missing = 5)	69 (27.3%)	21.8 - 32.8
Neurological Symptoms (missing = 5)	112 (44.3%)	38.1 – 50.4
Clinician Reported Variables		
HAND Diagnosis	119 (47.0%)	40.9 - 53.2

For demographic and HIV-disease specific data see Supplementary online data(16, 21)

Table II: Demographic, HIV-disease, neurological and functional impairment factors associated with DSM-IV depression in 2016 baseline cohort (n=253)

2016 variable	DSM-IV Depression 2016	No DSM-IV Depression 2016	Test and Significance
Psychosocial Factors			
Education (primary education not completed)	13 (31%)	78 (37.0%)	0.55 (χ^2) (p=0.46)
Education (primary school educated)	29 (69.0%)	133 (63.0%)	
Lives Alone	9 (21.4%)	34 (16.1%)	1.43 (χ^2) (p=0.49)
Unemployed	4 (9.5%)	25 (11.8%)	0.43 (χ^2) (p=0.93)
Mean Karnofsky Performance Scale (0-100%)	92.4%	93.9%	933.00 (M-W U) (p=0.77)
HIV-Disease Factors			
Mean CD4	438.6	530.2	2.00 (t-test) (p=0.17)
Mean Nadir CD4	203.6	196.1	-0.26 (t-test) (p=0.84)
Medication adherence (100% adherence)	23 (54.8%)	152 (72.0%)	5.34 (χ^2) (p=0.07)
Efavirenz	23 (54.8%)	111 (52.6%)	3.07 (χ^2) (p=0.80)
Self-Reported Neurological Impairment			
Balance Problems	2 (4.8%)	28 (13.3%)	2.48 (χ^2) (p=0.12)
Slow Hand Movements	3 (7.1%)	24 (22.4%)	0.70(χ^2) (p=0.40)
Neuropathy	11 (26.2%)	79 (37.4%)	2.11 (χ^2) (p=0.15)
Headaches	25 (59.5%)	136 (64.5%)	0.47 (χ^2) (p=0.49)

Normal Task Difficulties	10 (23.8%)	56 (26.5%)	0.12 (χ^2) (p=0.72)
Home Responsibilities Difficulties	2 (4.8%)	15 (7.1%)	0.30 (χ^2) (p=0.58)
Summary of Self-Reported Neurological Impairment			
Functional Impairment	10 (23.8%)	59 (28.0%)	0.31 (χ^2) (p=0.58)
Neurological Symptoms	14 (33.3%)	98 (46.4%)	2.44 (χ^2) (p=0.12)
Clinician Reported Variables			
HAND diagnosis	25 (59.5%)	94 (44.5%)	3.15 (χ^2) (p=0.76)

Table III: Outcomes at Follow Up (2018) of DSM-IV depression at Baseline (2016)

2018 Variable	DSM-IV Depression 2016	No DSM-IV Depression 2016	Test and Significance
Psychosocial Outcomes			
Life Event	15 (65.2%)	50 (36.0%)	7.65 (χ^2) (p=0.04)
Lives Alone	6 (26.1%)	31 (22.3%)	0.40 (χ^2) (p=0.53)
Unemployed	3 (13.0%)	13 (9.4%)	0.28 (χ^2) (p=0.60)
Depressed in 2018. (GDS definition)	7 (30.4%)	14 (10.1%)	7.25 (χ^2) (p=0.01)
Depressed in 2018. (DSM-IV definition)	3 (13.0%)	11 (7.9%)	2.48 (χ^2) (p=0.29)
Mean Karnofsky Performance Status (0-100%)	88.7%	94.2%	1174.50 (M-W U) (p=0.02)
HIV-Disease Outcomes			
Mean CD4 count (mm/l)	57 2.30	522.56	-0.86 (t-test) (p=0.14)
Mean Nadir CD4 count (mm/l)	252.97	190.81	-1.45 (t-test) (p=0.28)
Viral Load Unsuppressed	10 (43.5%)	42 (30.2%)	1.59 (χ^2) (p=0.45)
Medication Adherence (100% adherence)	22 (95.7%)	134 (96.4%)	3.39 (χ^2) (p=0.07)
WHO Stage 1/2	4 (17.4%)	20 (14.4%)	0.05 (χ^2) (p=0.83)
WHO Stage 3/4	19 (82.6%)	108 (77.7%)	
First Line Treatment	11 (47.8%)	73 (52.5%)	0.22 (χ^2) (p=0.88)
Second Line Treatment (missing = 10)	2 (8.7%)	15 (10.8%)	
Efavirenz (missing = 54)	7 (50.0%)	44 (46.8%)	1.29 (χ^2) (p=0.52)
Self-Reported Neurological Impairment			
Memory Problems	10 (43.5%)	41 (29.5%)	2.11 (χ^2) (p=0.35)
Concentration Problems	4 (17.4%)	7 (5.0%)	4.76 (χ^2) (p=0.03)

Difficulty Thinking Clearly	1 (4.3%)	2 (1.4%)	0.92 (χ^2) (p=0.34)
Cognitive Impairment	12 (52.2%)	42 (30.2%)	6.18 (χ^2) (p=0.10)
Balance Problems	6 (26.1%)	7 (5.0%)	11.85 (χ^2) (p=0.001)
Slow Hand Movements	7 (30.4%)	8 (5.8%)	14.31 (χ^2) (p<0.001)
Neuropathy	11 (47.8%)	41 (29.5%)	3.04 (χ^2) (p=0.08)
Headaches	8 (34.8%)	32 (23%)	1.47 (χ^2) (p=0.23)
Normal Task Difficulties	5 (21.7%)	19 (13.7%)	1.018 (χ^2) (p=0.31)
Home Responsibilities Difficulties	5 (21.7%)	14 (10.1%)	2.60 (χ^2) (p=0.11)
Summary of Self-Reported Neurological Impairment			
Functional Impairment	8 (34.8%)	27 (19.4%)	2.79 (χ^2) (p=0.25)
Neurological Symptoms	13 (56.5%)	47 (33.8%)	21.47 (χ^2) (p>0.001)
Clinician Reported Variables			
HAND Diagnosis	10 (43.5%)	86 (61.9%)	2.77 (χ^2) (p=0.10)
Symptomatic HAND	3 (13.0%)	29 (20.9%)	0.76 (χ^2) (p=0.38)

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Supplementary Table I – Self-Report Neurological Questionnaire

Initial Screen	1=yes, 2=no, 3=don't know, 9=missing	If yes, please describe your problems here: e.g. Further details of low mood etc.
B.3.1 Do you think you have problems with your memory?	**a.**	**b.**
B.3.2 Do you have difficulty with concentration, this means doing a task which takes a while. Are you able to pay attention to a sermon at the church or mosque, listen to a whole programme on the radio/news?	**a.**	**b.**
B.3.3 Do you have difficulty thinking clearly or making decisions?	**a.**	**b.**
B.3.4 Do you have difficulty with your balance or falling?	**a.**	**b.**
B.3.5 Do you have difficulty with slow hand movements?	**a.**	**b.**
B.3.6 Do you have loss of feeling in your hands or feet?	**a.**	**b.**
B.3.7 Do you have headaches?	**a.**	**b.**
B.3.8 Do you have difficulty in carrying out your normal day to day work? Please describe your difficulties here	**a.**	**b.**
B.3.9 Do you have difficulty in carrying out your home responsibilities? Please describe any difficulties or problems here	**a.**	**b.**

Supplementary Table II: Baseline (2016) demographic and HIV-disease data (n=253)

Sex (female)	183 (72.3%)
Age (md, range)	57 (50-79)
Education (primary school educated)	162 (64.0%)
Unemployed (missing = 6)	29 (11.5%)
Lives Alone (missing = 4)	43 (17.0%)
Current CD4 count (mm/l) mn, SD	526.5(255.2)
Nadir CD4 count (mm/l) mn, SD	197.2 (160.7)
Medication adherence (100% adherence)	175 (69.2%)
Tuberculosis	Current Infection: 5 (2.0%) Previous Infection: 42 (16.6%)
Empirical central nervous system infection treatment	Current: 8 (3.2%) Previous: 18 (7.1%)
BMI (mn, SD)	22.65 (4.59)
cART Regimen (missing = 17)	First-line: 211 (83.3%) Second line: 25 (9.9%)
On cART	242 (95.5%)
Efavirenz (missing = 8)	134 (53.0%)
WHO Stage (missing = 69)	1-2: 32 (12.6%) 3-4: 152 (60.0%)

Supplementary Table III: Demographic Characteristics of Follow-Up Cohort (those seen in 2016 and 2018, n=162)

	2016	**2018**
Sex (female)	183 (72.3%)	114 (70.4%)
Age (md, range)	57 (50-79)	59 (52-81)
Education		
Primary School not completed	91 (36.0%)	52 (32.1%)
Primary school educated	162 (64.0%)	110 (67.9%)
Unemployed (missing = 6)	29 (11.5%)	16 (9.9%)
Lives Alone (missing = 4)	43 (17.0%)	37 (22.8%)
Current CD4 count (mm/l)		
Mean	526.5	530.18
SD	255.2	255.17
Nadir CD4 count (mm/l)		
Mean	197.2	203.01
SD	160.7	167.88
Self-reported Medication Adherence (100% adherence)	175 (69.2%)	137 (84.6%)
Tuberculosis		
Current Infection	5 (2.0%)	0 (In previous 12 months)
Previous Infection	42 (16.6%)	
Central Nervous System		
Current Infection	8 (3.2%)	0 (In previous 12 months)
Previous Infection	18 (7.1%)	
BMI		
Mean	22.65	22.8
SD	4.59	4.9
ART Regimen		
First-line	211 (83.3%) (missing = 17)	84 (51.9%) (missing = 61)

Second Line	25 (9.9%)	17 (10.5%)
On ART	242 (95.5%)	
Efavirenz	134 (53.0%) (missing 8)	51 (31.5%) (missing = 3)
WHO Stage		
1-2	32 (12.6%)	24 (14.8%)
3-4	152 (60.0%) (missing = 69)	127 (93.2%) (missing = 11)
Viral Load Suppressed	Data not available in 2016	110 (67.0%) (missing = 11)
Psychiatric Medications (amitriptyline)	7 (2.8%)	6 (3.7%)

Supplementary table IV: Outcomes at Follow Up (2018) of having Depression by GDS Criteria at Baseline 2016 (supplementary data)

2018 Data	**GDS Depression at Baseline**	**GDS No Depression at Baseline**	**Test and Significance (p-value)**
Psychosocial Factors			
Life Event (missing = 3)	21 (67.7%)	44 (33.6%)	13.03 (χ^2) (p=0.001)
Lives Alone (missing=2)	8 (25.8%)	29 (22.1%)	0.26 (χ^2) (p=0.61)
Unemployed	7 (22.6%)	9 (6.9%)	7.03 (χ^2) (p=0.03)
Depressed in 2018 (GDS definition)	14 (45.2%)	7 (5.3%)	35.23 (χ^2) (p<0.001)
Depressed in 2018 (MINI definition)	3 (9.7%)	11 (8.4%)	1.73 (χ^2) (p=0.42)
Mean Karnofsky Performance Status (0-100%)	86.8%	95.0%	1287.50 (M-W U) (p<0.001)
HIV-Disease Factors			
Mean CD4 Count (mm/l)	549.48	525.56	-0.45 (t-test) (p=0.26)
Mean Nadir CD4 Count (mm/l)	252.97	190.81	-1.86 (t-test) (p=0.09)
Viral Unsuppressed	13 (41.9%)	39 (29.8%)	3.91 (χ^2) (p=0.14)
WHO Stage 1/2	5 (16.1%)	19 (14.5%)	

	(missing 2)	(missing 9)	0.49 (χ^2)
WHO Stage 3/4	24 (77.4%)	103 (78.7%)	(p=0.83)
Medication Adherence (100% adherence)	25 (80.6%)	112 (85.5%) (missing 3)	0.98 (χ^2) (p=0.32)
First Line Treatment	12 (38.7%)	72 (55.0%)	0.13 (χ^2)
Second Line Treatment	3 (9.7%)	14 (10.7%)	(p=0.72)
Efavirenz (missing = 54)	8 (42.1%)	43 (48.3%)	5.14 (χ^2) (p=0.08)
Self-Reported Neurological Impairment			
Memory Problems	13 (41.9%)	38 (29.0%)	2.37 (χ^2) (p=0.31)
Concentration Problems	4 (12.9%)	7 (5.3%)	2.26 (χ^2) (p=0.13)
Difficulty Thinking Clearly	1 (3.2%)	2 (1.5%)	0.40 (χ^2) (p=0.53)
Cognitive Impairment	15 (48.3%)	39 (29.8%)	5.84 (χ^2) (p=0.12)
Balance Problems	7 (22.6%)	6 (4.6%)	11.01 (χ^2) (p=0.001)
Slow Hand Movements	6 (19.4%)	9 (6.9%)	4.65 (χ^2) (p=0.03)
Neuropathy	14 (45.2%)	38 (29.0%)	3.00 (χ^2) (p=0.08)
Headaches	8 (25.8%)	32 (24.4%)	0.03 (χ^2) (p=0.87)
Normal Task Difficulties	7 (22.6%)	17 (13.0%)	1.83 (χ^2) (p=0.18)
Home Responsibilities Difficulties	8 (25.8%)	11 (8.4%)	7.34 (χ^2) (p=0.01)
Summary of Self-Reported Neurological Impairment			
Functional Impairment	12 (38.7%)	23 (17.6%)	6.69 (χ^2) (p=0.04)
Neurological Symptoms	16 (51.6%)	44 (33.6%)	11.01 (χ^2) (p=0.001)
Clinician Reported Variables			
HAND diagnosis	17 (54.8%)	79 (60.3%)	0.31 (χ^2) (p=-0.58)
Symptomatic	9 (29%)	23 (17.6%)	2.08 (χ^2)

HAND			(p=0.23)

Supplementary Table V: Studies Investigating the Longitudinal Prevalence of Depression in People Living with HIV

Author	**Country**	**Population**	**Prevalence at Baseline**	**Prevalence at follow-up**	**Mean Age**	**% on ART**	**Depression Criteria**	**Length of follow up**
(Rodkjaer et al., 2011)(37)	Denmark	Adults – general population	26.0%	16.0%	Data not available	80.0	Beck Depression Inventory II	3 years
(Olley et al., 2006)(29)	South Africa	Recently diagnosed adults	34.9%	26.0%	30	1.3	MINI	6 months
(Johnson et al., 1999) **(35)**	USA	IVDU	18.1%	16.2%	39	Data not available	Structured Clinical Interview for DSM-III-R	3 years
(Orlando et al., 2002)(55)	USA	Adults – general population	22.0%	18.6%	Data not available	Data not available	CIDI-SF and CIDI (DSM-IV criteria)	8 months
(Rabkin et al., 1997)(36)	USA	IVDU	26.0%	14.0%	38.5	Data not available	Structured Clinical Interview for DSM-III-R	3 years