# Can patients and their caregivers boost identification of HIV Associated Neurocognitive Disorder (HAND)?


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## KEY WORDS
People living with HIV, HIV associated neurocognitive disorder, mild neurocognitive disorder, caregiver



## ABSTRACT
HIV associated neurocognitive disorder (HAND) may be difficult to identify as signs and symptoms (S&S) are nonspecific.

**Objective**
To ascertain whether people living with HIV and their caregivers using a self reflective tool could identify S&S of HAND.

**Design**
This study was a nurse led prospective observational multi-site study using a quantitative design.

**Setting**
Participants were recruited from three sites in Sydney, New South Wales (NSW), Australia: an inner metropolitan HIV clinic, an inner metropolitan sexual health clinic and a suburban hospital HIV clinic.

**Subjects**
121 patients and 44 caregivers who attended ambulatory clinics providing HIV care.

**Main Outcome Measures**
Observing usual standard of care to follow patients who had formal neuropsychological testing and diagnosis of HAND.

**Results**
Sixty one percent of participants and 57% of caregivers identified more than four symptoms. Sixteen had neuropsychological exams; five were diagnosed with HAND. After changes to their medication regime all of those five showed an improvement in cognition. Of the remaining 11, four results were inconclusive, with some deficits noted.

**Conclusion**
Patients and caregivers stated the booklet helped them to reflect on behavior changes which they could subsequently discuss with their doctor. The booklet was considered useful to identify S&S which could indicate HAND.

## INTRODUCTION

HIV is treated with medications known as antiretroviral drugs which has had a substantial positive impact on morbidity and mortality for People Living with HIV (PLHIV) and has resulted in life expectancy approaching population norms for those individuals who have optimal adherence to HIV medications. (Clifford and Ances 2013). Yet, despite HIV virological suppression and immune recovery, studies suggest 30% of PLHIV are affected by HIV associated neurocognitive disorder (HAND), (Clifford and Ances 2013; del Palacio et al 2012; Heaton et al 2010) significantly impacting quality of life (Tozzi et al 2004).

In the 1980s, the clinical features of AIDS dementia complex (ADC) were those of a sub-cortical dementia characterised by cognitive impairment, behavioural abnormalities and disturbed motor function. With the introduction of antiretroviral medications, ADC largely disappeared from clinical practice, but now milder forms of cognitive impairment are being observed. In 2007, the classification for ADC was revised, and is now known as HAND. HAND is divided into three categories, each with varying degrees of disability impacting quality of life: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), which causes symptomatic disease, and HIV Associated Dementia (HAD) (Antorini et al 2007). This study focuses on the signs and symptoms (S&S) associated with MND.

MND affects the person's ability to perform activities of daily living such as preparing meals, managing finances, attending doctors' appointments and driving. It may also affect their social relationships and the ability to retain employment or be promoted. Caregivers can have a positive effect on the health and well being of PLHIV (Gisslen et al 2011) and may be well placed to notice any changes in the PLHIV. Signs and symptoms of MND may be subtle and are potentially normalised by PLHIV and may be difficult to detect by clinicians. Individuals may start to notice mild memory problems and slowness, difficulties in concentration, planning and multitasking (Schouten et al 2011; Heaton et al 2010; Grant 2008).

A booklet was developed (Trotter and Cummins 2008) to be used by patients and caregivers to reflect on whether the person was experiencing signs and symptoms which may indicate HAND. Information in the booklet focused on four key areas that affect cognition (memory, concentration, motor skills and social skills) for patients and their caregivers to reflect on any changes in cognition. Using the booklet enabled the caregiver to recognise potential signs and symptoms of MND. It should be noted that some PLHIV may be socially isolated (McDonald et al 2013) and not have the support of a caregiver and may have no one they can rely upon who may notice changes in their cognition including memory, motor function and social behaviour.

There are currently no biological markers for a definitive diagnosis of HAND (Atluri et al 2014). Studies suggest predictors of HAND are: past history of AIDS defining central nervous system disease (Fabiani et al 2013), other central nervous system disease (Valcour et al 2004), low CD4 cell count (Schouten et al 2011), drug and alcohol use (Fiala et al 2005), low education level (Tedaldi et al 2015), and Hepatitis C infection (Schouten et al 2012).

PLHIV with cognitive impairment including HAND, have been shown to be less adherent to HIV medication regimes. (Robertson et al 2010; Skinner et al 2009). This may lead to drug resistant HIV, resulting in their current medication regime becoming ineffective (Robertson et al 2010; Skinner et al 2009). Morbidity and mortality can then be affected as the person experiences poor health outcomes secondary to impaired adherence (Thames et al 2011).

If identified and treated early, using HIV drug treatment or changing the medication regimen to medications which have a higher CNS penetration via the blood brain barrier (Letendre et al 2010) may lead to improvement in previous cognitive changes related to MND thus improving outcomes for patients (Cysique et al 2009).

In addition as PLHIV age they may be at risk of other neurologic conditions associated with ageing such as vascular dementia and Alzheimer's disease (del Palacio et al 2012). Thus the complexity of neurological health for PLHIV may be on the increase. The prevalence of MND among PLHIV in Sydney, NSW is unknown. There is a paucity of literature regarding PLHIV's experiences of and their reflections that is consideration of any changes in cognition in the last 12 months and any signs and symptoms they are currently experiencing which may be indicators of HAND.

## METHOD

### Aim

To consider the value of patient and caregiver use of a self-assessment booklet in leading to early medical assessment of MND.

### Design

A quantitative study from a prospective observational multi-site study to explore the usefulness of a patient self-assessment booklet "HIV associated MND: How to recognise signs and symptoms" developed by two of the authors (Trotter and Cummins 2008) by assisting PLHIV and their caregivers in recognising any signs and symptoms of cognitive impairment as noted in the booklet. This is not a validated tool but was developed to explore whether patients were experiencing any signs and symptoms which could indicate HAND. The study period ran over 28 months from June 2012 to October 2014.

### Setting

The study was conducted at three outpatient sites within two Health Districts covering a greater part of Sydney, NSW, Australia.

Each site provides HIV specialist care: an inner city hospital based clinic, an inner city sexual health clinic and a suburban hospital based clinic. The inner city clinics are in the inner west of Sydney which has the second highest number of HIV diagnoses in NSW, Australia. A high proportion of patients seen at these clinics are men having sex with men (NSW HIV Strategy 2012-2015). The suburban hospital HIV clinic is in the outer suburbs of Sydney and cares for a high proportion of participants from culturally and linguistically diverse (CaLD) backgrounds.

### Participants

Participants were recruited whilst attending their regular multi-disciplinary consultation reviews at outpatient clinics at one of the three sites. Participants were eligible for inclusion if they were HIV positive over 18 years of age and they provided written consent at time of recruitment. Participants could nominate a caregiver to be invited to participate in the study. For the purpose of this study caregivers were considered unpaid individuals who provide practical, emotional or financial support to the person, such as partners, family members and friends. Initial recruitment was over a four month period in 2012.

Individuals were excluded if they were diagnosed with HIV in the last twelve months; had a preexisting identified cognitive impairment; were experiencing current social chaos or had inadequate English language skills. As depression may confound cognitive symptoms (Woods et al 2009), patients who had current untreated depression were excluded but became eligible once their depression was treated. Current alcohol and substance use was assessed and patients with dysfunctional use were excluded from the study until substance and alcohol use was addressed.

Participants completed a demographic questionnaire and were given the booklet "HIV associated MND: How to recognise signs and symptoms" (Trotter and Cummins 2008). The self assessment booklet was developed

by a HIV Psychiatrist and HIV Clinical Nurse Consultants, informed by literature review and professional experience. It was focus group tested for readability, clarity, design, flow and acceptability. The booklet has 36 items grouped into four categories of behaviours: concentration, memory, motor skills and social issues. Additionally the booklet had information in it noting how S&S may be misread as depression, ageing or being more stressed; but not to "panic" as having a clinical review would lead to a definitive diagnosis which could be treated.

Participants and caregivers were provided with the booklet and were asked to reflect on any changes experienced or observed over the last twelve months. If they noted any change in behaviour over the previous twelve months we asked them to respond "Yes" to each relevant item. They were contacted two weeks later via telephone to provide responses to items selected from the booklet.

A file audit was attended to ascertain specific risk factors for cognitive impairment including the participants' HIV viral load, CD4 T cell nadir and current CD4 T cell count. Current medication regimen was noted. The researchers observed the usual standard of care at medical consultations. Initially the researchers asked participants to discuss items identified in the booklet with their doctor during the next consultation. It became apparent that the discussion was not taking place as participants stated they were either "not remembering" to mention issues to the doctor, "did not think it was important" or there "was not enough time". The researchers intervened by transcribing the list of items selected by participant and/or their nominated carer, placing the list in a prominent place in the clinical notes to promote discussion at the next appointment. This resulted in increased discussions of the items selected.

As there was no other PLHIV self-reflective booklet available at the time to use as a guide, the researchers decided selection of four or more items would be flagged with medical practitioner for patient discussion. Previously clinical judgement and incidental anecdotal evidence from PLHIVs was relied on to discuss issues relating to HAND.

All neuropsychological testing was conducted by a trained clinical neuropsychologist. This procedure followed the usual required battery of tests required as a neuropsychological exam. The results were made available for the researchers to ascertain which participants completed the exam and final results. The clinical review process of participants diagnosed with MND was observed for changes in treatment prescribed by their doctor and the outcome of the treatment. Data entry was completed by one member of the team who was not involved in the recruitment process.

## STATISTICAL ANALYSES

Data was analysed using SPSS (V21 IBM Corporation Armonk, NYI, USA). Analysis included presentation of descriptive statistics, Chi Square tests, Mann Whitney and Kruskall Wallis tests as indicated.

## ETHICS

Ethics submission had been approved by Royal Prince Alfred Hospital Research Ethics Committee (X10-0354+ HREC/10/RPAH/618) and Liverpool Hospital Research Ethics Committee (SSA/11/LPOOL/203) Sydney Australia.

## RESULTS

Of 330 people screened for enrolment in the study 165 (50%) were ineligible including 30 (9%) who declined participation. At the suburban hospital site 30 people were not screened for enrolment due to limited staffing issues during study period which impacted on the overall number of participants able to be recruited at that site. Table 1 summarises the exclusion criteria of the 165 ineligible PLHIV.

**Table 1: Exclusion criteria of patients excluded**

| Criteria | Total |
|---|---|
| New Diagnosis of HIV | 12 |
| Pre-existing Ccognitive Impairment | 34 |
| Social chaos | 16 |
| Poor English | 44 |
| Drug and Alcohol Use | 16 |
| Current untreated depression | 13 |
| Declined | 30 |
| Total excluded | 165 |

In total 121 participants and 44 caregivers across the three sites were recruited (table 2).

**Table 2: Participants and Caregivers recruited**

| Participants Recruited | Total |
|---|---|
| Number of participants | 121 (100%) |
| Number of participants who identified 4 or more S&S | 74 (61%) |
| Number of caregivers | 44 (100%) |
| Number of caregivers who identified 4 or more S&S | 25 (57%) |

More than one third of participants (39%) noticed some behaviour change in themselves and 28 (23%) were concerned about these changes in behaviour.

The mean age of participants was 49 years old, range 25 to 75years. The median was also 49 age was normally distributed; <40 years (n=25), 41-50 years (n=48), 51-60 years (n=31), 61-70 years (n=16) and >71 (n=1). Sixty one per cent identified four or more S&S and of these four, after further investigation, were diagnosed with HAND but there was no difference in age in those diagnosed with HAND (mean 48) and those without HAND (mean 49) with a p value of 0.845. Ninety six per cent were men (116). Forty nine participants (40.5%) lived alone, 46 (38%) lived with a partner and 24 (20 %) lived in shared households. Two participants lived (2 %) with children.

**Depression**

Forty eight (39.7%) participants had a history of depression, which is consistent with the prevalence of depression in HIV positive populations (Grierson et al 2009). Thirty two (26.4%) were currently being treated for depression. Those with depression tended to have more symptoms selected from the booklet than those without current depression. P=0.056 Mann Whitney Test.

**HIV Information**

The median duration of HIV infection of participants was 10 years, range (0 – 29) which indicated the participants had been infected for some time and therefore be at increased risk of developing co-morbid conditions. The CD4 T lymphocyte cell count is a marker of antiretroviral treatment responses and HIV disease progression. The participants' median CD4 count was $590x10^7$ (10 – 1720) which is within normal limits, indicating that participants have adequate immunity; CD4 nadir count is the lowest it has ever reached and low CD4 nadir count is also a predictor of HAND, the median CD4 nadir was well below normal CD4 count at $180\ x10^7$ (0 – 750); median prescribed antiretroviral medications therapy was six years (0 – 28).

**Risk factors for non-HIV related cognitive impairment**

Many PLHIV have co-morbid conditions. A review of participants' clinical notes revealed some risk factors for non-HIV related cognitive impairment were documented in all notes (table 3). Of these factors, none were statistically significant.

**Table 3: Identified from clinical notes patient risk factors for cognitive impairment**

| Current Conditions | Yes | P Mann Whitney | P t test |
|---|---|---|---|
| Hepatitis C virus | 10 (8.3%) | 0.046 | 0.159 |
| Hypertension | 31 (25.6) | 0.443 | 0.155 |
| Prescribed Antihypertensive drug | 29 (24%) | 0.734 | 0.280 |
| Hypercholesterolemia | 79 (65.3%) | 0.803 | 0.452 |
| Hyperlipidaemia | 61 (50.4%) | 0.203 | 0.406 |
| Sleep Apnoea | 5 (4.1%) | 0.498 | 0.361 |
| Diabetes | 7 (5.8%) | 0.078 | 0.033 |
| Current smoker | 38 (31.4) | 0.010 (Kruskal Wallis) | Anova |

### Antiretroviral medications

Ninety four per cent (114) were currently taking antiretroviral medications. Of these, 30% (n=36) were on a once daily co-formulated single pill regimen, and 33 (n=40) took three or more pills per day.

Eleven percent (n=13) had missed more than two doses of medications in the last month. There was a trend for a higher number of symptoms in the group who were not adhering to their medications P=0.070 Mann Whitney Test.

### Caregivers

Seventy seven participants (64%) did not nominate a caregiver to be contacted. Six caregivers declined to be involved. The suburban hospital recruits (n=14) did not identify any caregivers. Of the caregivers identified (n=44), 82% (n=36) were male and 18% (n=8) were female. The relationship of the caregiver to the PLHIV varied: twenty-eight were male same sex partners, six were female partners of men, three were husbands of women, one was a mother, one a son, four were male friends and one was a female friend. Forty two percent (n=15) of the caregivers identified as PLHIV.

The most reported symptoms by both caregivers (47%) and participants (67%) was “being mentally tired at end of day” and caregivers (64%) and participants (67%), “have you noticed you don’t go out socially as much as you used to?”

### Neuropsychological examination

Twenty three (31%) of the 74 participants who identified more than four S&S from the booklet were offered clinical neuropsychological examination following consultation and clinical review by their doctor. Seventy percent (n=16) underwent the usual standard battery of tests performed in the clinical neuropsychological examination and 30% (n=7) declined testing (table 4). Four participants (25%) of the 16 that had completed a clinical neuropsychological examination were diagnosed with MND as a result of these examinations.

**Table 4: Neuropsychological Exam Results**

| Number of Neuropsychological exam (n=16) | Results of Neuropsychological exam |
|---|---|
| 5 (31%) | Inconclusive, ongoing monitoring recommended |
| 7(44%) | Within normal limits (1 depression, 1 sleep apnoea) |
| 4 (25%) | MND diagnoses (medication regimen optimised, subsequent improved cognition noted) |

## DISCUSSION

MND can have a detrimental impact on the health and well-being of PLHIV. As part of the HAND spectrum, MND may be difficult to identify because key signs and symptoms of MND may be subtle and often the PLHIV and their caregivers may believe signs and symptoms are attributable to other issues such as ageing, stress and/or lifestyle factors.

There were no previous studies regarding PLHIV and/or Caregivers' self-reflection of signs and symptoms of cognition to guide us. The researchers chose the identification of four or more symptoms by either participants or caregivers as a cue to monitor subsequent investigations and current standard of care. The 61% of participants and 57% of caregivers who identified four or more symptoms supported adoption of using the booklet to reflect on changes in the participants behaviour.

Caregivers are well placed to notice changes in cognitive behaviour (Glissen et al 2011). Many stated they welcomed being involved in the study and that using the booklet to help reflect on the PLHIVs behaviour enabled them to start a discussion regarding behaviours they had noticed but did not know how to raise with the person. In addition some of the caregivers also identified as PLHIV and this may impact on future support if they as the caregiver also become ill or cognitively impaired.

Many of the participants live alone and did not identify caregivers who may be well placed to notice any changes in cognitive behaviour. At one site, none of the participants identified a caregiver. A majority (70%) of these participants were MSM who were married to women. Their lifestyle did not include HIV culture of gay men in Australia, perhaps best illustrated by one participant "We don't talk about the HIV much, and I sure don't want to mention this". The clinician needs to be more vigilant in asking PLHIV without identified carers about cognition. The combination of PLHIV reflecting regularly on their behaviour and staff with a therapeutic relationship with the PLHIV, including knowing their social situation may combine to improve identification of impairment (as PLHIV may underrate signs and symptoms). As this population age they may become isolated socially (McDonald et al 2013) and the relationship with their clinician may become very important for asking questions about cognition. Discussion of cognition and memory should be incorporated and normalised into an annual review of HIV care, and may result in early detection (Wright and Watson 2012). This may reduce fear and apprehension of results from neuropsychological testing and enhanced discussion of signs and symptoms (several participants declined testing due to fear of the outcome and being labelled cognitively impaired).

Regular reflection by the PLHIV and their caregiver may assist in early interventions for HAND screening and diagnosis. Many of the participants had long standing HIV which may place them at risk of developing HAND even though their HIV was well managed (Antorini et al 2007). The average age of participants was 49 years and as they age they may be at risk of developing co-morbidities such as heart disease which may affect cognitive impairment and may need to be closely monitored for signs and symptoms of cognitive impairment. The greatest co morbidity risk factors for cognitive impairment identified in the participants were vascular risk factors, such as: current nicotine smoking (31%), those with hypercholesterolaemia (65%), hyperlipidaemia (50%), or hypertension (25%) (table 3). These figures point to the need to monitor patients and develop strategies to improve management of co-morbidities such as smoking cessation. In addition successful management of co-morbidities may help improve HAND outcomes (Wright and Watson 2012).

The signs and symptoms of depression may confound MND diagnosis so it is important to screen the PLHIV for this (Grierson et al 2009). Forty per cent of participants in this study had a previous history of depression, 26% were currently being treated for depression and 9% identified signs and symptoms of depression, and so were excluded from the study until reviewed by their doctor. The group who were currently being treated for depression were non-significantly more likely to have S & S of cognitive impairment ($p=0.056$). Many PLHIV were excluded from this study due to current untreated depression, substance use issues and language difficulties. Early detection and treatment of depression, providing assistance with depression and substance issues and developing resources in different languages would support improvement of rates of PLHIV being identified with and treated for MND.

Ninety four per cent of the participants were prescribed antiretroviral medications. Of these 33% were taking

more than three antiretroviral drugs. The researchers did not enquire about other medications. Pill burden may be a factor in adherence (Robertson et al 2010; Skinner et al 2009). Eleven per cent had missed > 2 doses of medications in the last month. This group had a non-significantly higher number of items from the booklet (P=0.070).There is a potential for a closed feedback loop whereby the patient with adherence problems may, as a result of the poor adherence, suffer further cognitive decline, leading to further impairment of adherence.

This study enabled some people who would otherwise been missed to be identified and referred for neuropsychological assessment. Using this booklet PLHIV were able to reflect and use the booklet to report to clinicians, leading to neuropsychological testing. Several had their treatments changed by their doctor to a regime that had improved central nervous system penetration and had improvements in cognition when subsequently reviewed (table 4). Thirty per cent of PLHIV offered neuropsychological testing declined. Nurses are well placed to explore the reasons for declining and facilitating understanding of the improved outcomes formal testing could facilitate. The therapeutic relationship between patient and nurse may promote an open conversation, allowing the nurse to provide information to the PLHIV enabling further assessment and investigations.

Initially participants did not divulge items they had noticed from the booklet with their doctor as they did not think it was important, forgot or ran out of time. Nurses are well placed to discuss this with patients prior to their appointment with their doctor, to ask if the person has noticed any recent changes in cognitive symptoms or behaviours. Information from this discussion can be documented and brought to the attention of the doctor prior to the consultation. Nurses can use the booklet to initiate discussion and with regular questioning normalise the issue with the patient. Scheduled annual review of the patient would also be of benefit, utilising the initial documentation as a baseline for noticing changes in behavior and cognition.

## LIMITATIONS/CHALLENGES

There were several challenges during this study.

There was no HIV negative matched comparison group for this study. This study was designed to follow the patient through their usual standard of care at the clinic they attended. Future studies could include a comparison group.

As there was no validated self reflective tool available we relied on professional judgement and incidental anecdotal evidence from PLHIVs to discuss issues relating to HAND. The researchers decided to flag if four or more items from the booklet were selected.

The small number of patients diagnosed with HAND (four) limited further analysis particularly in relation to age and further study is needed to clarify if there is a distinction between HAND and other age related neurocognitive or psychogeriatric conditions.

Exclusion of people who had inadequate English language skills made many participants ineligible for the study. Translation of the resource into community languages would assist in recruitment of this group in future.

## IMPLICATIONS FOR PRACTICE

Nurses providing care and support to PLHIV should be aware of HAND and what questions to ask, and should further explore patients' experience. A booklet exists which can be used by clinicians, patients and their carers to start a conversation about any signs and symptoms the PLHIV may be experiencing - assisting the PLHIV to reflect on recent changes in behaviour such as memory and concentration problems which could affect their quality of life. Reflection of change may prompt further exploration by their doctor of cognitive decline.

Early recognition and treatment may have a positive impact on the health and well being of the patient by reducing signs and symptoms and restoring independence.

As PLHIVs age and are at risk of developing other diseases of the brain, a HAND diagnosis should be considered in a neurological setting.

## CONCLUSION

PLHIV are experiencing signs and symptoms of cognitive impairment which can affect their quality of life. HAND is a diagnosis of exclusion and PLHIV and their caregivers can have a major part in recognising signs and symptoms. Self-reflection is very important, as is reflection from caregivers.

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