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ORIGINAL RESEARCH

# A screening algorithm for HIV-associated neurocognitive disorders

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**Background**

HIV physicians have limited time for cognitive screening. Here we developed an extra-brief, clinically based tool for predicting HIV-associated neurocognitive impairment (HAND) in order to determine which HIV-positive individuals require a more comprehensive neurological/neuropsychological (NP) assessment.

**Methods**

Ninety-seven HIV-positive individuals with advanced disease recruited in an HIV out-patient clinic received standard NP testing. A screening algorithm was developed using support vector machines, an optimized prediction procedure for classifying individuals into two groups (here NP-impaired and NP-normal) based on a set of predictors.

**Results**

The final algorithm utilized age, current CD4 cell count, past central nervous system HIV-related diseases and current treatment duration and required approximately 3 min to complete, with a good overall prediction accuracy of 78% (against the gold standard; NP-impairment status derived from standard NP testing) and a good specificity of 70%.

**Conclusion**

This noncognitive-based algorithm should prove useful to identify HIV-infected patients with advanced disease at high risk of HAND who require more formal assessment. We propose staged guidelines, using the algorithm, for improved HAND therapeutic management. Future larger, international studies are planned to test the predictive effect of nadir CD4 cell count, hepatitis C virus infection, gender, ethnicity and HIV viral clade. We recommend the use of this first version for HIV-infected Caucasian men with advanced disease.

**Keywords:** antiretroviral therapy, diagnosis algorithm, HIV/AIDS, HIV-associated neurocognitive disorder, mathematical model

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## Introduction

The clinical management of HIV-positive persons is increasingly complicated in the era of combination antiretroviral therapy (CART). One aspect of management that requires extensive training relates to the early identification of neurocognitive complications of HIV infection. In many countries the general practitioner or the HIV physician is often the primary patient's interlocutor [1]. Without specific screening using procedures that are still relatively lengthy or require specific training, especially for interpretation [2], physicians may sometimes overlook patients in need of further neurological evaluation.

In the CART era, the prevalence of neurocognitive impairment remains high (up to 50% [3]) and HIV-associated neurocognitive disorder (HAND) has shifted towards a milder clinical presentation [4]. Such a mild clinical presentation can escape detection without formal neurological assessment and neuropsychological testing [5]. HAND, even in its mild form, is independently predictive of death [6] as well as HIV-associated dementia

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[7]. Short-term outcomes include significant impact on independence in daily activities including employment [8], and perhaps most importantly medication adherence [9]. The availability of a tool that can easily be used to predict HAND is therefore necessary.

Here we propose a screening algorithm for HAND that was developed in a sample of 97 HIV-positive individuals with advanced disease. This algorithm was based on risk factors that have been documented for HAND: age [10], educational achievement [11], plasma viral load [12], previous central nervous system (CNS) HIV-related insult [13], haemoglobin levels [14], HIV infection duration [15], CART CNS penetration characteristics [16] and duration of current CART [17].

The development of the screening algorithm was based on support vector machine (SVM) methodology. Because the aim of our study was to provide a simplified algorithm from a complex set of predictors, SVM was the most appropriate procedure [18]. The SVM has been shown to be extremely robust in solving prediction problems while handling large sets of predictors [18]. It is an alternative to more standard statistical techniques such as logistic regression and in certain situations has been found to be superior to logistic regression for finding a robust fit with fewer predictors [18–21].

## Methods

### Participants

HIV-positive individuals from the out-patient clinics at St. Vincent's Hospital, Sydney, Australia, were invited to participate in a prospective study of the neurological/neuropsychological (NP) complications of HIV disease. The inclusion criteria were advanced HIV disease (Centers for Disease Control and Prevention stage C3; see Cysique e*t al.* [22] for details), being on CART (at least three antiretroviral drugs) and being clinically stable. Therefore, this cohort was composed of individuals who had been historically immunosuppressed.

Detailed information on this cohort has been published elsewhere [22]. Briefly, for advanced HIV-infected individuals, mode of infection was homosexual contact in 93% of cases (94 of 101), injecting drug use (IDU) in two cases, transfusion in one case, unknown in two cases and heterosexual contact in two cases. The injecting drug users denied current drug use and this was confirmed by their clinician. Nineteen patients with a previous HIV-related brain disease included 16 patients with AIDS Dementia Complex (ADC) stage 0.5 or 1, of whom two had toxoplasmosis in addition to ADC, one had progressive multifocal leukoencephalopathy in addition to ADC and one had cryptococcal meningitis in addition to ADC; and three had cryptococcal meningitis. These 19 patients did not differ from the other patients in their neuropsychological performance.

**Table 1** Demographic, clinical, treatment and laboratory characteristics for the HIV-infected individuals with advanced disease

| Characteristic | |
|---|---|
| *n* | 97 |
| Age (years) (mean ± SD) | 48.86 ± 9.41 |
| Education level (years total) (mean ± SD) | 14.09 ± 2.85 |
| Sex (% male) | 100 |
| English-speaking background (%) | 98 |
| Estimated HIV duration (years) (mean ± SD) | 11.94 ± 4.77 |
| Past HIV-related brain diseases [% (*n*)] | 19.6 (19) |
| Date of initial CART (mean ± SD) | 1996 ± 1.5 |
| Duration of current CART regimen (months) (mean ± SD; range; median) | 18 ± 17; 1–62; 12 |
| CNS penetration effectiveness of current HAART (mean ± SD; range; median) | 1.88 ± 0.86; 0–3.5; 2 |
| Nadir CD4 count (cells/μL) (mean ± SD) | 71.96 ± 62.55 |
| Nadir CD4 count ≤ 100 cells/μL (%) | 68 |
| Current CD4 count (cells/μL) (mean ± SD) | 347.03 ± 230.29 |
| Current CD4 count ≥ 350 cells/μL (%) | 48.5 |
| Plasma HIV RNA ($\log_{10}$ copies/mL) (mean ± SD; min–max) | 2.86 ± 1.44; 1.69–5.87 |
| Undetectable plasma HIV RNA (< 50 copies/mL) [% (*n*)] | 52.6 (51) |
| Haemoglobin (g/L) (mean ± SD) | 139.95 ± 17.42 |
| Depression (DASS standardized score) (mean ± SD) | 0.41 ± 1.27 |

CART, combination antiretroviral therapy; CNS, central nervous system; DASS, Depression Anxiety Stress Scale; HAART, highly active antiretroviral therapy; SD, standard deviation.

Thirty seronegative controls were also enrolled in this study to develop a standard NP reference (Table 1). The group of HIV-negative controls was recruited in the same Sydney metropolitan area as the HIV-positive sample. On average, they did not differ from the HIV-positive sample for age [mean ± standard deviation (SD): HIV-positive, 48.51 ± 9.32 years; HIV-negative, 47.40 ± 9.39 years; $P = 0.54$], education (HIV-positive, 14.05 ± 2.85 years; HIV-negative, 15.00 ± 3.08 years; $P = 0.15$), gender (all male) or premorbid intelligence quotient (HIV-positive, 115.71 ± 8.64; HIV-negative, 117.40 ± 6.61; $P = 0.32$). Their overall NP performance was well within the normal range (mean ± SD: 0.001 ± 0.20), providing a valid reference for definition of NP impairment in the HIV-positive group.

The HIV-negative individuals were seronegative, on a screening test (enzyme-linked immunosorbent assay) for HIV-1-specific antibody, at least 3 months prior to the examination and screened for significant neurological or psychiatric diseases. An interview on medical history was conducted in order to exclude participants with neurological or psychiatric disease (epileptic disorder, traumatic brain injury with loss of consciousness > 30 min, or current major

depressive episodes) or any significant medical history (cardiovascular diseases). All denied a history of IDU.

CNS penetration effectiveness (CPE) was computed using Letendre *et al.* [16] criteria. Depression Anxiety Stress Scale (DASS) scores are reported as standard scores derived from published normative data [23]. A score of + 1 (compared with controls) represents a mild degree of mood complaints, + 2 moderate and + 3 severe.

Individuals were excluded from the study if they had a history of a current psychotic disorder, a current neurological disease (current CNS opportunistic infections, current HIV-associated dementia, current neurological disorder unrelated to HIV, active syphilis, or head injury with loss of consciousness >30 min) or a current drug use disorder. Six individuals were hepatitis C virus (HCV) positive, of whom four had received anti-HCV treatment and three had cleared the virus. The other two were asymptomatic. Therefore, the effect of HCV as a predictor of cognitive impairment could not be tested.

A total of 101 participants were enrolled in the study. All clinical and laboratory information was recorded coincident with the examination. Haemoglobin was recorded retrospectively and incomplete data were found for four patients. Therefore, 97 HIV-positive subjects were included in this analysis (see Table 1).

All participants signed an informed consent form and the affiliated research institutions and their ethics committees approved the research protocol.

## Procedure

All participants were examined with a standard NP battery including 14 individual NP measures (see Cysique e*t al.* [22] for details). In addition, the DASS [24] was administered in order to measure mood status.

## Data analysis

### *NP-impairment definition*

Raw scores were transformed into standard *Z*-scores using the mean and SD for the HIV-negative controls as reference [23]. NP impairment was defined as follows: 2 SD below the control mean in at least two neuropsychological measures [25]. Using this NP-impairment definition, we found that 37.1% of individuals were classified as 'NP-impaired' in the HIV-positive sample (36 of 97) and 6.7% in the control group (two of 30) ($P = 0.0015$).

### *The SVM Method*

SVMs attempt to separate two groups, A and B, based on a vector of $n$ predictors [1]. The aim is to determine a vector $w \in \mathbf{R}^n$ and a constant $\gamma$ such that for each of the data points $x_i$ belonging to group A, $x_i^T w - \gamma \geq 1$, while for data points $x_i$ belonging to group B, $x_i^T w - \gamma \leq -1$. When the sets A and B are not completely separable in this manner the method incorporates the errors in separation $\xi_i$ for each data point. For data points $x_i$ belonging to A we assign the value $y_i = +1$, while for $x_i$ in B we assign the value $y_i = -1$. Optimal separation of the two sets consisting of $m$ data points in total is then achieved through the optimization problem

$$\begin{aligned} &\underset{w,y}{\text{minimize}} \frac{1}{2}||w||^2 + v\sum_{i=1}^{m}\xi_i \\ &\text{subject to } y_i\left(x_i^T w - \gamma\right) + \xi_i \geq 1, \quad i = 1, \ldots, m \\ &\xi_i \geq 0, \quad i = 1, \ldots, m \end{aligned}$$

where $v$ is a tuning parameter. This problem is modified to include a measure of the number of predictor variables used in the model by penalizing nonzero values of each of the components of the vector $w$. This aspect is termed 'feature selection' so that the optimal solution of the SVM method balances the accuracy of prediction with choosing the fewest number of predictors from the initial set of $n$.

The SVM method used, $pq-$SVM, was a modification of the Lagrangian Support Vector Machine (LSVM) method of Mangasarian and Musicant [26], incorporating feature selection [27]. The inequality for prediction of NP impairment using the nonnormalized original data was scaled to a range of values of approximately − 10 to + 10, for uniformity between scenarios.

Approximately two-thirds of all individuals did not exhibit HAND, and with this bias the method favours accuracy in prediction of this group. However, the preference for HIV management is to predict those with HAND with the extra expense related to extensive neurological testing of those without HAND outweighed by availability of treatment to those with NP impairment. We therefore weighted prediction of those with HAND to at least 70% accuracy by duplicating the data from 30 randomly chosen individuals with HAND and adding these to the original data set.

The application of SVM to a data set consists of two steps. The first, called the 'training phase', consists of using the SVM on a subset of the data to determine optimal values of the parameters $w$ and $\gamma$. The second, called the 'testing phase', involves applying this choice of parameters to the remainder of the data set to determine the accuracy of the procedure. The accuracy of the training phase is the percentage of data points within the training set that have $y_i(x_i^T w - \gamma) \geq 0$. The accuracy of the testing phase is similarly defined. The training and testing phases were conducted using two-thirds of the data randomly chosen for the training set and the remaining one-third for the

testing set. As these methods require the selection of tuning parameters such as $v$ in the SVM formulation above, a preliminary training and testing phase was first carried out to determine the tuning parameters and predictor coefficients $w$ that achieved maximal testing efficacy. The tuning parameters required in the $pq-$SVM method $(v, \lambda_1)$ were calculated over the grid $(2^i, 2^j)$ where $i,j \in \{-5,-4,\ldots,10\}$ [27,28]. The steps of randomly choosing two-thirds of the data for training, the calculation of optimal parameters over the grid of values, and the choice of tuning parameters and predictor coefficients that achieve maximal testing efficiency were then repeated 1000 times. The aim of the repeated simulations was to ensure that there were scenarios that achieved a range of predictive capabilities for those without NP impairment, as we wished to limit the number of false positives. The optimal predictor coefficients for each scenario were determined from the best of these 1000 simulations that also achieved at least 70% efficiency (or closest to this constraint) in predicting those with impairment and those without.

We applied the SVM with feature selection to the data for the 97 HIV-positive individuals with advanced disease, 36 of whom had been assessed as having HAND, while the remainder were assessed as not having HAND. The total data comprised 11 factors that have been associated with the presence of HAND or NP performance: age (years), education level (total years of schooling), duration of HIV infection (years), current haemoglobin level (g/L), current CD4 T-cell count (cells/μL), current plasma $\log_{10}$ HIV RNA ($\log_{10}$ HIV-1 RNA copies/mL), current plasma viral detection (HIV RNA $\geq 50$ copies/mL), past CNS HIV-related diseases (past CNS opportunistic infection or HIV-associated dementia (HAD) resolved at least 6 months prior to study entry), CART CPE [16], depressive complaints and duration of current CART (months). 'Plasma viral detection' and 'past CNS HIV-related diseases' were categorical variables taking a value of 1 when the response was positive. We were not able to test the effect of nadir CD4 cell count because the range of this variable was restricted in our cohort as advancement of the disease was a criterion of inclusion.

For the SVM calculations, the data were first normalized (mean 0 and SD 1), so that the weights with the largest magnitude indicate predictors with the greatest impact on NP prediction.

## Results

The factors with the greatest impact on prediction of NP impairment were age (weighting 0.33) and *current* CART duration (weighting −0.16) (Table 2). A positive value indicates that a larger value of the component is associated with NP impairment, while a negative value indicates that a lower value is associated with NP impairment. Hence older age and past CNS disease are likely indicators of NP impairment, with positive weightings, while shorter CART duration, lower CD4 cell count and, for this group, shorter HIV duration and lower viral load are more likely to indicate NP impairment.

**Table 2** Optimal support vector machine (SVM) coefficients for normalized data and accuracy of predictions

| Variable | SVM coefficients with predictors including $\log_{10}$ HIV RNA | SVM coefficients with predictors including detectable/undetectable HIV RNA |
|---|---|---|
| Age | 0.33 | 0.36 |
| Education level | 0 | 0 |
| Haemoglobin | 0 | 0 |
| Current CD4 | −0.12 | −0.10 |
| $\text{Log}_{10}$ plasma HIV RNA | −0.10 | – |
| Detectable HIV RNA | – | 0 |
| HIV duration | −0.11 | 0 |
| Past CNS diseases | 0.13 | 0.10 |
| Current CART duration | −0.16 | −0.28 |
| NP impairment accuracy (sensitivity) | 78% | 78% |
| NP nonimpairment accuracy (specificity) | 70% | 70% |

A positive value indicates that a higher value of the component is associated with neurological/neuropsychological (NP) impairment, while a negative value indicates that a lower value is associated with NP impairment.
CART, combination antiretroviral therapy; CNS, central nervous system.

In terms of the nonnormalized original data, and based on this set of possible components, NP impairment is predicted to occur when the following expression holds:

$$\begin{aligned}\text{NP impairment:}\quad & 0.351 \times \text{age} - 0.005 \times \text{CD4} - 0.681 \\ & \times \log_{10}\text{HIV RNA} - 0.225 \\ & \times \text{HIV duration} + 3.356 \\ & \times \text{CNS disease} - 0.098 \\ & \times \text{CART duration} - 9.8748 \geq 0.\end{aligned}$$

where the terms refer to age (years), current CD4 T-cell count (cells/μL), current $\log_{10}$ HIV RNA (copies/mL), HIV duration (years), past occurrence of CNS disease (1 if this has previously occurred and 0 otherwise), and current CART duration (months). NP impairment is predicted not to occur when this expression is negative. The accuracy of this assessment with this data set was 78% for correctly predicting NP impairment (sensitivity), and 70% for correctly predicting NP nonimpairment (specificity). Hence this assessment, based solely on clinically available data, will fail to recognize NP impairment when it is present 22%

of the time, and will incorrectly infer NP impairment when it is not present 30% of the time.

We next assessed NP impairment based on the same set of predictors but with $\log_{10}$ HIV RNA replaced by whether current HIV RNA (copies/mL) was above (1) or below (0) the 50 copies/mL detection limit for each individual. Once again, age (weighting 0.36) and current CART duration (weighting $-0.28$) were the dominant components (Table 2). Also consistent in indicating NP impairment between the two scenarios were past occurrence of CNS disease and lower current CD4 cell count.

The predictor of NP impairment under this scenario, and using the original nonnormalized data values, was given by

$$\text{NP impairment: } 0.377 \times \text{age} - 0.004 \times \text{CD4} + 2.502 \times \text{CNS disease} - 0.165 \times \text{CART duration} - 14.990 \geq 0$$

where, as before, the terms refer to age (years), current CD4 T-cell count (cells/μL), past occurrence of CNS disease (1 if this has previously occurred and 0 otherwise), and current CART duration (months). With this expression, the accuracy of the NP-impairment prediction was 78% and the accuracy of the prediction of NP nonimpairment was also 70%, equivalent to the model accuracy using $\log_{10}$ HIV RNA. Hence this assessment, based solely on clinically available data, will fail to recognize NP impairment when it is present 22% of the time, and will incorrectly infer NP impairment when it is not present 30% of the time.

Both SVM models yielded medium-to-large negative correlations (Spearman $r = 0.50$; $P < 0.0001$) between the model's predicted values and the average $Z$-score, meaning that better predictions of NP-impaired status were associated with greater severity of cognitive deficits.

The same models were also tested including self-reported depressive symptoms and CART CPE. Including data on self-reported depressive symptoms for the scenario where $\log_{10}$ HIV RNA was included only yielded an accuracy of 75% for the prediction of impairment and an accuracy of 72% for the prediction of NP nonimpairment. For the scenario where detectable *vs.* undetectable HIV RNA was included, along with depressive symptoms, the best model achieved an accuracy of 72% for NP impairment and an accuracy of 70% for NP nonimpairment. Because of the increased variability that results from the inclusion of an extra predictor that does not greatly contribute to classification, these values were worse than the accuracies when depressive symptomatology was omitted. Therefore, self-reported depressive symptoms did not improve the SVM prediction accuracy.

Including data on CART CPE also failed to improve the prediction. For the scenario where $\log_{10}$ HIV RNA was included, the accuracy of the prediction was 75% for impairment and 72% for NP nonimpairment. These same accuracies were also achieved for the scenario where detectable *vs.* undetectable HIV RNA was used. Hence inclusion of CPE did not improve prediction accuracy.

## Discussion

Our study was conducted with the intention of generating an extra-brief tool to assist HIV physicians in referring HIV-positive persons at risk for NP impairment. We believe that our study provides a preliminary but robust solution to this first objective. Indeed, we found that our SVM-derived models yielded adequate prediction accuracy for NP impairment (sensitivity 78%; $n = 28/36$) and NP nonimpairment (specificity 70%; $n = 43/61$). These figures are certainly adequate for use of the algorithm as an adjunct clinical tool.

Moreover, we believe that the predictions were quite good in comparison with predictions of HAND provided by brief paper-and-pencil NP instruments. Davis *et al.* [28] reported 70% sensitivity and 71% specificity for the HIV-dementia scale. Carey *et al.* [29] showed 78% sensitivity, 85% specificity and 83% overall prediction accuracy using two selected NP tests. The California Computerised Assessment Package (Calcap), a brief cognitive computerized test, yielded 68% sensitivity and 77% specificity [30]. Lastly, the brief computerized battery CogState demonstrated 81% sensitivity, 70% specificity, and an overall prediction accuracy of 77% [31].

These accuracy rates provide preliminary support for application of these models in a clinical setting. In addition, this algorithm can be easily implemented on a web-interface platform (under construction) for which the HIV physician will only have to input the necessary characteristics [for example when using the model determined from detectable levels of HIV RNA the required characteristics are: age in years; current CD4 T-cell count; presence or absence of past CNS HIV-related diseases (yes or no); and current CART duration in months]. The expected duration of the screening (computation of the algorithm including data entry with interactive instructions) is about 3 min. Here we have shown that it is the inclusion of easily ascertainable clinical factors that makes the algorithm practical. However, while the inclusion of the factors might be obvious, the relative weighting of each is certainly not.

This study also contributes to the body of evidence on the use of SVM as a robust tool for data classification problems [18]. SVM methods have been increasingly used in a wide variety of medical classification problems. In certain instances they can prove superior in terms of classification accuracy to standard methods such as logistic

regression, especially in being able to extract key predictors [18–21] that can then be used in the simplified algorithm.

Some of the model findings were in accordance with previous findings in the literature. Cross-sectional age was associated with NP-impairment status prediction, as expected. A lower current CD4 T-cell count was associated with a higher likelihood of being predicted to be NP-impaired, consistent with past findings [14]. Previous CNS HIV-related insults were associated with NP-impairment status prediction. This was also demonstrated in previous studies which included CNS opportunistic infections [32] or previous HAD [7] or both [22]. Lastly, a shorter duration of current CART was associated with NP impairment. This suggests that, when NP impairment is to be predicted cross-sectionally, the duration of treatment is an important factor as it affects the estimate of *current* CART efficiency in terms of NP functions. There is now evidence that a window of 6 months and possibly up to 1 year is necessary to obtain maximal benefit [33]. This finding also confirms that stability of NP function is more likely in individuals who are also stable on their CART [17].

The CPE did not improve the overall prediction accuracy of our models. It is important to verify if this may have had a substantial effect on the findings, as patients received various CART regimens with varying degrees of CNS penetration. It should be noted that the benefit of a high CPE was demonstrated in an NP-impaired cohort only (see [34] for a review), which differed from the cohort used in the current study.

We also found that depressive complaints did not substantially improve our model, and this is in accordance with studies that showed that major depressive disorders as well as self-reported depressive symptoms were not associated with NP impairment in HIV-positive persons [35,36].

When considering the dichotomous categorization of plasma viral load, our results were consistent with the current literature in showing a dissociation between cross-sectional plasma viral load and cognitive impairment in CART-treated individuals [37]. When using $\log_{10}$ HIV RNA, we found a small but negative SVM coefficient for $\log_{10}$ HIV RNA, meaning that a lower viral load was associated with the NP-impairment status prediction. In this case it is likely that the individuals who had higher viral loads were also more likely to have just started treatment. Additionally, of the 97 individuals analysed here, 51 had undetectable viral loads and these were assigned a value of 50 $\log_{10}$ copies/mL. As these individuals all had the same value, the SVM separation method could not distinguish on this factor alone for these individuals and any separation achieved through $\log_{10}$ HIV RNA was partly attributable to the 51 individuals with the same viral load but also to the remaining 46 individuals each with a different viral load. Although $\log_{10}$ HIV RNA tended to show a positive correlation with age when all viral loads were included ($P = 0.3$; $\rho = 0.1$), including only individuals with a detectable viral load produced a correlation with age that was not significant but was negative ($P = 0.7$; $\rho = -0.06$). Hence the negative weighing for viral load may be attributable more to

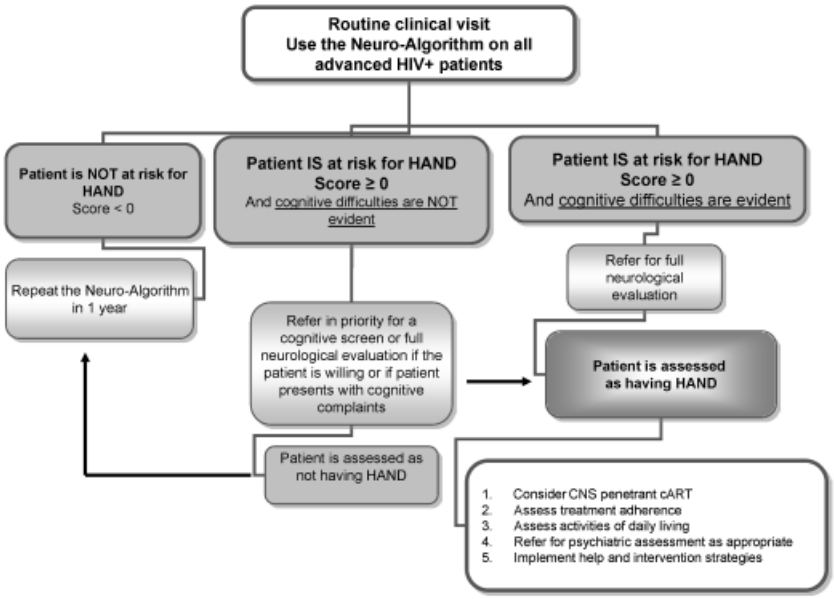


**Fig. 1** Suggested algorithmic approach for the detection of cognitive impairment in HIV-infected individuals.

the inverse correlation with age than to any underlying effect of low but detectable viral load on NP impairment. Because of this, we recommend that the algorithm is used with the input of detectable *vs.* undetectable viral load.

Also, for the model using $\log_{10}$ HIV RNA, we found, contrary to our expectations, that shorter HIV duration was associated with NP impairment. This inconsistency partly arises as a result of the determination of HIV duration as many individuals were not diagnosed with primary HIV infection. HIV duration was measured from diagnosis rather than infection, and older individuals are generally diagnosed later [38]. Thus some of the weight that arises from short HIV duration may really be associated with an older cohort that has been diagnosed late. This interpretation is supported by the data, as HIV duration was significantly positively correlated with age ($P = 0.045$; $\rho = 0.2$). However, there was a group of older individuals with shorter HIV duration. Indeed, the median age of those that had been diagnosed with HIV infection for $<5$ years was 56.5 years, while for those that had been diagnosed with HIV infection for more than 15 years the median age was only 51.5 years.

Taken together, our results should be interpreted in the context of an observational study composed of men with advanced HIV disease, reflecting the HIV epidemic demographic characteristics in Australia. In other words, this first algorithm may be most validly applied to HIV-positive men with similar clinical characteristics. To facilitate the use of our algorithm, we propose staged guidelines for its implementation, accompanied by guidelines for improved therapeutic management in HAND (Fig. 1).

To improve the generalizability of our approach, further validation of the algorithm will require larger, international cohorts inclusive of women and HIV-positive individuals with less advanced disease, with a wide range of nadir and current CD4 cell counts, and ideally using comorbidity factors such as substance use, cardiovascular diseases and coinfection with HCV or other relevant diseases pertinent to limited-resource settings (e.g. malaria and tuberculosis).

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