

# Neuropsychological profile in a specific cohort of HIV patients infected postnatally: a cross-sectional study

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**Abstract:** HIV-associated neurocognitive disorders (HANDs) are one of the most important complications of HIV infection reported in the current literature. Although HANDs have been closely studied in vertically infected HIV populations or in specific subgroups such as drug abusers or homosexuals, they have been completely understudied in hemophilia patients with HIV, infected through transfusions postnatally. For this reason, it seemed interesting to evaluate the presence of HAND in this specific population. The aim of this work is to present a study protocol aimed at assessing the neuropsychological profile of HIV+ hemophilia patients compared with that of HIV– hemophilia patients. This is the first European study to evaluate the neuropsychological profile of HIV+ adult hemophiliacs prospectively.

**Keywords:** neuropsychological profile, neuropsychology, HIV, cognitive disorders, hemophilia

## Background

Human immunodeficiency virus (HIV) is highly neurovirulent.<sup>1</sup> Prior to widespread availability of highly active antiretroviral therapy (HAART), the prevalence of HIV-associated cognitive impairment has been estimated to lie between 6% and 30%, and this impairment could progress quickly to dementia or death.<sup>2–4</sup> The introduction of HAART in 1996 has resulted in the suppression of the systemic HIV-1 viral load and improvements in survival for patients with HIV infection.<sup>5,6</sup> Since 2009, the term combination antiretroviral therapy (cART) has largely supplanted the more commonly known HAART, particularly among researchers and clinicians. It employs the use of three or more antiretroviral drugs, either taken individually or in fixed-dose combinations. Antiretroviral therapy (HAART/cART) has also been associated with an improvement in cognitive performance<sup>6</sup> and a decreased incidence of HIV dementia.<sup>2,7</sup> With treatment, the frequency of dementia has been attenuated, but it still remains uncertain whether the frequency of specific cognitive impairments in HIV infection has changed. HIV-associated neurocognitive disorders (HANDs) have not been yet eliminated, and they represent one of the most important complications of HIV infections.<sup>2,8,9</sup> They are the result of neural damage caused by HIV replication and immune activation<sup>10</sup> and are generally divided into three categories: 1) asymptomatic neurocognitive impairment, 2) mild neurocognitive disorder (MND), and 3) HIV-associated dementia.<sup>11</sup> Asymptomatic neurocognitive impairment is detected when neuropsychological tests show HIV-associated impairments, but routine and daily functioning is not compromised. MND is detected when neuropsychological tests show HIV-associated impairments and mild impact in routine and daily functioning. HIV-associated dementia is detected when neuropsychological tests show important HIV-associated impairments and a severe

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impact on daily functioning. This impairment significantly limits one's ability to function day-to-day at work, home, and during social activities. MND appears to be the most common type of HAND.<sup>11</sup> Despite its name, even mild cognitive problems can interfere with everyday functioning and reduce the quality of life. Estimates indicate that as many as 50% of HIV+ individuals display some degree of cognitive impairment<sup>10</sup> when impairment is derived from comparisons with normative performance standards.<sup>6,10</sup>

While HAND are well studied in HIV-seropositive (HIV+) patients infected perinatally, these disorders remain comparatively understudied in the HIV+ population infected postnatally, suggesting that research should address the potential for neurocognitive complications in this cohort of patients. Indeed, neuropsychological impairments have been mainly studied in HIV-seropositive (HIV+) patients infected postnatally during the earliest period of life of the child (eg, through breast milk) or in specific cohorts of adults such as homosexuals and drug users, but much less is known regarding individuals infected postnatally.<sup>12</sup> As revealed in the literature, in the cohort of homosexuals and drug users, patients show different neuropsychological impairments, but these profiles are difficult to describe because they are often complicated by a myriad of confounding factors, which may be present in these patients, such as the abuse of substances (eg, alcohol, cocaine, and opiates),<sup>13,14</sup> emotional disorders (eg, anxiety and depression),<sup>5</sup> and different risk behaviors.<sup>4</sup>

Furthermore, studies on HIV+ individuals infected postnatally, as is the case with hemophilia patients, are quite rare. This group of patients is quite distinct from other cohorts, the children infected postnatally through transfusions have a different path of the infection than those who were infected perinatally,<sup>15-17</sup> and they generally do not present certain psychosocial vulnerabilities, which are sometimes related to perinatal infection and which may impact as covariate variables. Some such factors are, for instance, the severe illness or death of a parent due to AIDS or a lower socioeconomic status. Finally, the growth of patients infected postnatally may be different from the growth of patients infected perinatally because of the differences in the rate of brain growth; for instance, Rubin et al<sup>18</sup> found different patterns of neurobehavioral development depending on age of infection, and Brouwers et al<sup>19</sup> found differences in structural brain abnormalities between perinatally and transfusion-infected children.

The majority of individuals infected postnatally are hemophiliac patients. Due to the fact that HIV was not well

known before 1985, many hemophilia (A/B) patients became silently infected through contaminated blood infusion and hence were at risk of developing AIDS.<sup>20</sup> Patients with hemophilia are treated with injections of whole blood or other processed blood derivatives. Repetition of this treatment in the past exposed the hemophiliacs to the risk of bloodborne infections as HIV.<sup>21</sup> Today, it is estimated that 60%–70% of people with hemophilia were infected with HIV in this way between 1979 and 1985.<sup>22</sup>

Hemophilia is a rare coagulation disorder in which a crucial clotting factor in blood is missing either partly or completely.<sup>23-26</sup> Being a sex chromosome–gene-related bleeding disorder, it occurs primarily in the male population. There are two main types of hemophilia. In the more common hemophilia A (eight of ten), patients are missing or have low levels of clotting factor VIII, whereas in hemophilia B patients are missing or have low levels of clotting factor IX.<sup>27</sup> Most of the literature on HIV and hemophilia is derived from the Hemophilia Growth and Development Study (HGDS),<sup>28</sup> which studied the longitudinal effect of the HIV infection on adolescents. The main publications of HGDS, for example, Sirois et al,<sup>29</sup> Whitt et al,<sup>30</sup> and Loveland et al,<sup>17</sup> revealed that most of the asymptomatic cohort of HIV+ children and adolescents did not vary considerably from HIV– hemophilic controls on several neurocognitive tests at baseline. However, as shown in follow-up data of HGDS patients by Tombaugh et al<sup>31</sup> and by Loveland et al<sup>20</sup> over a period of 5 years, the majority of these young patients showed an important regression in neuropsychological performance, which was highly correlated to declines in immune functioning status. This regression, however, was not clearly associated with HIV infection, but it was associated with socioeducational variables such as school absenteeism and poorer academic achievement. Although the HGDS represents an important study in pediatric population, it is a quite dated study, which began before the introduction of HAART. Moreover, studies are totally underrepresented in the adult population, with mixed and confusing results.<sup>32</sup> The only two exceptions from literature data found no significant differences at the Mini-Mental State Examination between patients with hemophilic HIV and healthy controls;<sup>33,34</sup> the only significant alterations in patients with hemophilic HIV were found in patients suffering from spontaneous brain hemorrhage (microbleeds). Studies on adult hemophiliacs HIV+ are also novel because the survival rate of such patients has increased over recent decades as a result of the development of new therapies.

Based on these considerations, the present study protocol aims to evaluate the presence of HAND in HIV+ adult

hemophiliacs in comparison with a control group of HIV–hemophiliacs by administering a full neuropsychological battery.

## Objectives

The primary objective of this study is to compare the neuropsychological profiles of patients with both hemophilia and HIV versus the profiles of patients with hemophilia who are not HIV infected.

The secondary objective is to evaluate the influence of age and other sociodemographic data (education and working status) in the cognitive profile of both groups.

The influence of sociodemographic variables has been extensively investigated in the HIV population; however, it has been underestimated and not evaluated in the specific group of HIV+ adult hemophiliac patients.

## Design

The study will apply the STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) procedures for observational studies. The STROBE checklist criteria for cohort, case–control, and cross-sectional studies will be fulfilled.<sup>35</sup> This is an observational, cross-sectional, prospective study to be conducted in three hemophilia centers: Milan, Naples, and Rome.

The study will last for 12 months, and it will involve 45 patients with a ratio of 1:2 (15 HIV+ hemophiliacs and 30 HIV– hemophiliacs).

The group of HIV+ hemophiliacs will have the following characteristics:

- Age  $\geq 30$  years
- Currently in cART regimens (including nucleotide reverse transcriptase inhibitors, nonnucleotide reverse transcriptase inhibitors, protease inhibitors, or integrase inhibitors)
- Diagnosis of hemophilia A or hemophilia B or von Willebrand disease
- Hemophilia diagnosis with any type of severity (severe hemophilia, Factor VIII [FVIII] level  $<1\%$ ; moderate hemophilia, FVIII level ranging from  $1\%$ – $5\%$ ; mild hemophilia, FVIII level ranging from  $6\%$ – $30\%$ )
- Diagnosis of HIV.

The control group will have the same characteristics, except for the diagnosis of HIV.

The criterion of age ( $>30$  years) was chosen based on the fact that patients were particularly exposed to the infection during the period 1979–1984 when the sources of FVIII level were contaminated with HIV.<sup>36</sup>

The protocol will exclude patients presenting the following characteristics:

- Presence of central neurological disorders and/or severe psychiatric disorders (diagnosed before/after HIV) that limit the execution of test assessment
- Presence of acute internal diseases
- Abuse of recreational drugs or alcohol interfering with everyday life in the opinion of the physician
- Concomitant use of antipsychotic treatment (eg, major tranquilizers) interfering with everyday life in the opinion of the physician.

## Psychological assessment Neuropsychological evaluation

Participant (HIV+ and HIV–) hemophiliacs will complete the Italian Brief Neuropsychological Exam,<sup>37</sup> including the measurement of six major cognitive domains. In this battery, standardized tests are included. The battery contains the most important standardized test for cognitive functions and is widely used in the Italian context.<sup>38,39</sup> Attention will be measured by Trail Making Test, which is a neuropsychological test of visual attention and task switching.<sup>37</sup> Working memory will be detected with the digit-span memory test using the Letter-Number Sequencing of the Wechsler Adult Intelligence Scale, third edition (WAIS-III),<sup>40</sup> while phonemic memory will be assessed by the Verbal Fluency test.<sup>41</sup> Abstraction, that is the ability of logical reasoning and generalization of concepts, will be measured by the Italian Test of abstraction of the Brief Neuropsychological Exam.<sup>37</sup> Language will be measured with the short version of the Token Test, which is a valuable measure for assessing receptive language.<sup>42</sup> Executive functions will be assessed with the Clock-Drawing Test.<sup>43</sup> Finally, visual recognition will be detected through the Rey Tangled Lines Test.<sup>44</sup>

## Evaluation of daily life activities

All patients will undergo a specific ad hoc interview for deterioration in daily living activities.

## Study procedures

### Schedule of appointments

Regular appointments are expected to be performed at the three Hemophilia Centers, starting with the appointment in which written consent of the patient to data collection is obtained.

The patient identifier will consist of two parts, by which the patients will be uniquely identified:

- Center number (two digits)
- Patient identification number within center (two digits).

A participating list will be provided for each center. For each specific center number, each enrolled patient will be consecutively documented.

## Statistical analysis

This is a noninterventional study, and the statistical approach is exploratory in nature. With the  $\alpha$  error of 5%, and the power ( $1-\beta$ ) of 80% assuming a prevalence of impairment of 50% in hemophilia HIV cases and of 10% in the control group (patients with hemophilia HIV), the sample size estimated to conduct the study is, at least, 15 cases and 30 controls with a case:control ratio of 1:2. In order to avoid bias in the inclusion phase, a complete list of the patients will be collected, and they will be randomly chosen by using a random number generator.

Non-HIV patients will be matched with HIV patients by age ( $\pm 5$  years). The presence of HAND will be defined according to the cutoff normal value limits for each test, based on the internal control group (non-HIV hemophilic patients). HAND scores (for each test and as a global score) will be measured according to a standardized method as mild, moderate, and severe impairment.

Analyses will be performed using SPSS Version 21 statistical software (StataCorp LP, College Station, TX, USA). Alpha will be set at 0.05, two tailed. Sociodemographic and clinical data (age, job status, and education) will be descriptively analyzed by means of frequency, median, mean, standard deviation, range, and confidence intervals. Differences in demographic variables between HIV groups (HIV+ and HIV-) will be examined using analysis of variance for continuous variables and Pearson's  $\chi^2$  tests or Fisher's exact test for categorical variables. Years of education, job status, and age will be included as covariates in the analyses of neurocognitive data. The aging effect is modeled using both dichotomous baseline age groups (young, <45 years; old,  $\geq 45$  years) and continuous age.

We are also interested in analyzing effect sizes. In order to calculate Cohen's  $d$ , the participants will be split into four groups: younger (age < 55 years) HIV-, older (age 55 years and above) HIV-, younger HIV+, and older HIV+. Following these analyses, participants' scores will be converted into T-scores corrected for age, education, and job status to compare scores to established norms.

Raw scores for the individual cognitive tests will be converted to population-based  $z$  scores (ie, individual score minus the group mean, divided by the group standard deviation) using raw score distributions from the clinical sample

(ie, older HIV-infected sample) for standardization and comparison purposes.

## Ethical conduct and good clinical practice

This study will be conducted in accordance with national laws. Ethics committees (ECs) and national agencies will be informed and their approval sought. Data protection regulations will be strictly adhered to at all times (eg, Directive 95/46/EC). This study will be carried out completely independent of any medicinal treatment recommendations. Patients will be assessed and treated according to the individual decision of the attending physician. The study will not provide any recommendations with regard to diagnostic procedures or dosages, time of intake, or the strength of any medication. All decisions are to be made by the physician in the best interest of the patient's care.

## Ethics committee and authority

Before the study begins, the noninterventional plan, written data protection form(s), and/or other appropriate documents will be submitted to the EC, in accordance with local legal requirements. The patients will be provided with appropriate forms for obtaining written consent for data collection. In the case of minors, a written consent for the collection of data from the respective patient must also be obtained from the patient's parents or a legally authorized representative, as applicable, after adequate explanation of the purposes of this observational study and the objectives of data collection.

## Conclusion

The last 2 decades have borne witness to dramatic improvements in the availability and quality of treatment for persons with HIV. Accordingly, a considerable number of these patients now live longer. In the context of hemophilia, the introduction of virus-inactivated plasma-derived coagulation factors and recombinant products has revolutionized the care of people with hemophilia, improving their health-related quality of life and life expectancy. However, living with two severe conditions such as HIV and hemophilia is challenging. As with any medical condition, it is very important to evaluate the psychological and cognitive processes related to multiple diseases and multiple treatments.<sup>45-49</sup> This study is unique in the field of hemophilia, and it will offer an in-depth evaluation of the neuropsychological profile and a psychoemotional assessment of this particular cohort of patients with HIV.

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## Disclosure

The authors report no conflicts of interest in this work.

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