Interruptions of antiretroviral therapy in human immunodeficiency virus infection: are they detrimental to neurocognitive functioning?

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Because interruptions of antiretroviral treatment may entail clinical risks for human immunodeficiency virus (HIV)-infected individuals, we investigated their impact on neurocognitive functioning. Cross-sectional study was carried out, comparing HIV-infected persons who had interrupted antiretroviral therapy in the past (interruption group, IG) with persons who had never discontinued therapy (noninterruption group, NIG). Interruption was defined as the discontinuation of highly active antiretroviral therapy (HAART) for more than 15 days after previous treatment of at least 15 days. All the participants were on therapy. Demographic, clinical, and neurocognitive variables were assessed. The primary end point was the percentage of people with neurocognitive impairment. The score in different neurocognitive domains was a secondary end point. A total of 83 subjects participated in the study (IG: n = 27; NIG: n = 56). Demographic and clinical characteristics were balanced between the groups, except for years since HIV diagnosis (IG, 13.8; NIG, 10.2 [P = .003]). The percentage of people with neurocognitive impairment was significantly higher in the IG group (IG, 59.25%; NIG, 33.92% [P = 0.02]). As for scores in neurocognitive domains, individuals in the IG showed worse neurocognitive functioning, and significant differences in attention/working memory and information processing speed were found. The adjusted analysis supported the unadjusted analysis. In this study, a higher prevalence of neurocognitive impairment was detected in HIV-infected persons who had interrupted antiretroviral therapy in the past. Additionally, neurocognitive functioning was observed to be more impaired in the same individuals. Further studies should examine the potential negative effects of antiretroviral therapy interruptions on neurocognitive functioning. Journal of NeuroVirology (2010) 16, 208–218.

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Introduction

Patients infected with human immunodeficiency virus (HIV) continue to experience impairment of neurocognitive functioning. Although the incidence of most neurological complications has decreased since the introduction of highly active antiretroviral therapy (HAART), the prevalence of HIV-associated dementia (HAD) has not declined, and the incidence of milder neurocognitive disorders, such as mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI), has increased (Cysique et al., 2004; Sacktor et al., 2002; Tozzi et al., 2005a). Both observations are related to the persistence of HIV in the central nervous system (CNS) (Muñoz-Moreno et al., 2009; Spudich et al., 2005) and the inability of current antiretroviral therapy to effectively protect the CNS (Cysique et al., 2006; Tozzi et al., 2007), as well as the emergence of new potential risk factors, such as aging (Becker et al., 2004), nadir CD4 cell count (Muñoz-Moreno et al., 2008), and coinfection with hepatitis C virus (HCV) (Hilsabeck et al., 2005).

Treatment interruption in chronically HIV-infected individuals is often based on the patient’s decision, although it has also been applied as a therapeutic strategy by clinicians to reduce antiretroviral-associated toxicity, improve quality of life, and reduce the economic burden of antiretroviral therapy for public health systems. However, despite these potential advantages, there is evidence of significant risks for individuals discontinuing treatment and of an association with increased morbidity and mortality (Danel et al., 2006; El-Sadr et al., 2006).

As little is known about the effect of treatment interruptions on neurocognitive functioning, we conducted a study to compare neurocognitive functioning in HIV-infected patients who had interrupted antiretroviral therapy with that of patients who had not. We assessed the prevalence of neurocognitive impairment and measures of neurocognitive functioning.

Results

A total of 136 patients were informed and invited to participate in the study. Of these, 124 accepted and 83 fulfilled the study criteria (see Figure 1). Of the 83 eligible participants, 27 patients were assigned to the interruption group (IG) and 56 to noninterruption group (NIG).

The demographic, emotional, and clinical characteristics of the participants are shown in Table 1. The study groups were statistically comparable, except for time since HIV diagnosis, which was greater for IG participants (IG, 13.8; NIG, 10.2 [P = .003]). Although some of the remaining demographic, emotional, and clinical variables showed differences in the distribution between groups, none of them reached statistical significance. The greatest differences were seen in time on treatment (IG: 8.2; NIG: 7 [P = .09]) and the scores for anxiety (IG, 47; NIG, 40 [P = .06]). Other virological and immunological parameters such as plasma viral load, nadir CD4 cell count, or current CD4 count did not show statistical significance. There were a total of 55 interruptions in the IG (sexually transmitted infections [STIs]: 41.8%, patient’s decision [36.3%], and toxicity [21.8%]). The remaining characteristics of the interruptions are shown in Table 2.

Neurocognitive impairment affected 16 patients (59.2%) in the IG and 19 patients (33.9%) in the NIG (P = .02). The percentages for HANDs in both groups are shown in Table 1. The distribution was similar between groups, except for HAD, which was higher in the IG.

With regard to the scores representing neurocognitive domains, the comparison between groups revealed significant differences in the following functions: attention/working memory, specifically in digit span forward (IG, 46.8; NIG, 51.3 [P = 0.03]) and digit span backward (IG, 48.1; NIG, 53 [P = 0.008]), and information processing speed in the Symbol Digit Modalities Test (SDMT) written score (IG, 46; NIG, 50.6 [P = .01]). These scores therefore indicated worse functioning in the IG. In fact, the remaining neuropsychological outcomes revealed that all scores were lower in the IG than in the NIG, thus indicating a general poorer functioning in this group, although the difference did not reach statistical significance. The differences in the scores representing neurocognitive domains are shown in Table 3.

An additional post hoc subanalysis was performed including all the scores in each neurocognitive domain assessed, and the mean was calculated for each of them. This was compared between groups, and the results showed statistically significant differences in attention/working memory. The outcomes of this analysis for the IG and NIG, respectively, were as follows: attention/working memory, 48.9 and 52.2 (P = .02); information processing speed, 49.6 and 51.8 (P = .24); verbal memory, 50.7 and 51.2 (P = .82); learning, 47.4 and 50.4 (P = .30); executive functions, 49.3 and 51.5 (P = .18); verbal fluency, 45.7 and 49.1 (P = .07); and motor function, 51.9 and 54.8 (P = .22). Figure 2 summarizes the results for cognitive and motor functions in the form of a graph.

Because the study groups were not completely equivalent in terms of clinical variables, specifically with regard to time since diagnosis of HIV infection, a regression model was applied to assess the differences between neurocognitive scores, adjusting for time since diagnosis of HIV infection. This model revealed that significant differences between groups were maintained in the same cognitive and motor scores (digit span forward, P = .03; digit span backward, P = .01; and the SDMT written score, P = .02).