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MAJOR ARTICLE

The Presence of Human Immunodeficiency Virus-Associated Neurocognitive Disorders Is Associated With a Lower Adherence to Combined Antiretroviral Treatment

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Background. Human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) are defined according to their diagnostic degrees as follows: asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia. Because high adherence to combined antiretroviral therapy (cART) is required to maintain viral suppression among HIV-infected patients, it is important to investigate the impact of HAND on medication adherence. Our study hypothesis was that patients with HAND had a lower medication adherence than patients who did not have HAND.

Methods. This was an observational, exploratory, 2-center pilot study of patients who had a state-of-the-art neurocognitive assessment performed between January 2011 and June 2015 while also being followed at their respective adherence clinics. Adherence was measured with electronic monitors. Patients' sociodemographic characteristics, HIV viral load, and CD4 counts were retrieved from the Swiss HIV Cohort Study database. At each time *t*, adherence was computed as the proportion of patients taking medication as prescribed at that time.

Results. We included 59 patients, with a median (Q1, Q3) age of 53 years (47–58) and 39 (66%) were male participants. Twenty-two patients (35%) had no neurocognitive deficits, 16 (27%) patients had HAND, and 21 (35%) patients had non-HAND (mostly depression). Implementation over 3 years showed a significant decline (50%) in medication adherence among patients diagnosed with HAND in comparison with patients who had a normal neuropsychological status or a non-HIV-related cognitive deficit (implementation stayed 90% during follow-up).

Conclusions. Our findings support the hypothesis that HAND is associated with reduced cART adherence.

Keywords. HIV; HIV-associated neurocognitive disorders; medication adherence.

People living with human immunodeficiency virus (HIV) remain vulnerable to neurocognitive disorders (NCDs) despite an undetectable HIV viral load [1]. Human immunodeficiency virus-associated NCDs (HAND) are defined according to their severity as follows: asymptomatic neurocognitive impairment (ANI), mild NCD (MND), and HIV-associated dementia (HAD) [2]. Despite the significant decline in the incidence of HAD due to the introduction of combined antiretroviral therapy (cART), the prevalence of ANI and MND has increased by 30%–50% [3–5]. The neuropathogenesis of HAND remains unclear, although several factors such as the HIV infection itself [6], cART toxicity [7], and aging [8] are possible explanations.

Medication adherence is generally defined as the extent to which patients follow their medication regimen as prescribed by their healthcare providers [9]. It has 3 phases: initiation, which marks the start of treatment; implementation, which marks the extent to which the patient follows the dosing regimen; and discontinuation, which marks the interruption of treatment [9]. Nonadherence can occur in any of those phases, including premature interruption of treatment, defined as nonpersistence, or suboptimal implementation [10, 11]. There are several ways of monitoring medication adherence including pill counts, patient self-reports, and electronic monitors (EMs), which is the gold standard [9]. Nonadherence to antiretroviral (ARV) treatment is associated with virologic failure, the development of drug-resistant mutations, and a higher risk of mortality [12–14]. Therefore, a better understanding of the predictors of poor adherence is needed.

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To date, few studies cross-sectional in nature have used sensitive measures of medication adherence and neurocognitive function testing to investigate the association between HAND and cART adherence [15–18]. Nonetheless, using electronically measured medication adherence over 6 months, Becker et al [19] revealed longitudinal changes in neurocognitive function in the areas of attention and working memory, speed of information processing, learning and memory, verbal fluency, executive functioning, and motor speed. Our goal is to describe medication adherence longitudinally using EMs data for HIV patients on whom neurocognitive assessment testing was performed at university hospitals in Lausanne and Bern in Switzerland. Our study hypothesis is that there is an association between a HAND diagnosis and medication adherence.

METHODS

Data Sources

The Swiss HIV Cohort Study (SHCS), an ongoing multicenter prospective observational study for interdisciplinary HIV-related research, includes 69% of all HIV-positive patients in Switzerland [20]. All sociodemographic and clinical laboratory variables were extracted from the SHCS database on the date of neurocognitive assessment or within a range of 2–3 months before for data that were not available on the exact date (eg, laboratory results). To identify patients having neurocognitive assessments, we referred to 2 research databases: one is from a multidisciplinary (infectious diseases specialist, neuropsychologist, neurologist, psychiatrist and radiologist) Neuro-HIV outpatient clinic that was established in 2011 [21] of patients with cognitive complaints that can result in alterations in memory, attention, and reasoning; the other is from the Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study (nested within the SHCS), which began in 2013 and included HIV patients aged 45 years and older, with or without neurocognitive complaints, who presented for a neuropsychological exam, bone densitometry, and metabolic assessment every 2 years for 4 years [22]. Because the neurocognitive assessment testing began in 2011, we had 1 test result per patient available, which did not allow for evaluating the temporal causality between longitudinal adherence and NCDs. However, we assume that NCDs mostly occurred in patients before detection by neurocognitive testing. Due to the small number of patients relative to neurocognitive category, we could not evaluate adherence relative to neurocognitive category. Instead, we evaluated only the presence of a HAND diagnosis.

A medication adherence support program exists at the community pharmacy of the Department of Ambulatory Care and Community Medicine, University of Lausanne, in collaboration with the Infectious Diseases Service of the University Hospital. Medication adherence to each ARV drug is monitored via EMs (MEMS; Aardex MWV Healthcare, Sion, Switzerland), combined with manual pill counts, and motivational interviews. Electronic adherence data are shown to the patient as feedback, and a report is issued to the physician after each interview [23]. Patients initiating their cART, or patients with adherence difficulties anytime during their therapeutic pathway, are referred to this program by their Infectious Diseases physician. In Bern, the medication adherence intervention is performed at the Infectious Disease Service at the University Hospital and delivered by a nurse. All patients have only 1 component of their cART monitored electronically for a period of 3 months at the beginning of follow up. Some patients with adherence difficulties are again included in the program after the initial period.

Selection of Study Participants

In 2016, we cross-checked 5 databases to identify participants: the databases of the adherence program in Lausanne and Bern, the SHCS database, both databases of the Neuro-HIV multidisciplinary outpatient clinic, and the NAMACO study. We included all patients with electronically monitored adherence data and who were found either in the Neuro-HIV multidisciplinary outpatient clinic or the NAMACO databases. Longitudinal electronic measurements of adherence to ARV were assessed from 2008 to 2015, before neurocognitive assessment in all patients, except for 2 who were assessed before the initiation of electronic adherence monitoring. All participants were on cART.

Measures and Data Collection

The standardized neuropsychological assessment, inspired by the international START study [24], covers 7 cognitive domains: memory, attention, speed of information processing, executive functions, language, motor skills, and sensory-perceptive abilities. The neuropsychological test series used in this study consists of 9 tests that provide both quantitative and qualitative measures for a range of cognitive abilities. The tests are as follows: Hopkins Verbal Learning Test-Revised, Color Trails 1 and 2, WAIS-IV Digit Symbol Test, Five-point Figural Fluency Test, WAIS-IV Digit Spans Forward and Backward, Grooved Pegboard Tests, Finger Tapping Test, Victoria Stroop Test, and Semantic Verbal Fluency Test. Scales rating mood (CES-D) and daily life functioning (IADL including subscales from the PAOFI questionnaire) were also administered. During the visit to the Neuro-HIV multidisciplinary outpatient clinic with a trained neuropsychologist, neuropsychological evaluation was individually adapted in terms of cognitive and behavioral complaints, age, and socioeducational level. Each individual visit to the Neuro-HIV multidisciplinary outpatient clinic lasted 2 hours or more.

Medication adherence was measured using EMs (MEMS; Aardex MWV Healthcare) that use a pressure-activated microprocessor in the medication pill box that automatically records the date and time of each opening per single ARV drug. The key measures in the EM data system include patient identification

(ID), EM monitor ID, drug name, prescribed doses per day, the opening event day and time, and the start and stop dates of the monitoring period. Data were retrieved from the monitor using a specially designed communication module connected to a password-protected computer at the University Community Pharmacy in Lausanne and at the university hospital in Bern. Patients regularly visited the pharmacy (at least once per trimester), during which time they were asked whether they had periods of pocket dosing (ie, taking out medication for later use), whether they missed doses (and whether it was voluntary or involuntary), or whether they had nonmonitored periods (NMPs) due to hospitalization. In addition, pharmacists performed a manual pill count of the number of pills remaining in the pillbox since the patient's last visit. The pill count information allowed us to reconcile the EM data by comparing the values of electronic adherence as recorded by EMs to adherence as calculated by the pill count. This was not performed for the data in Bern because the intervention does not involve a pill count. However, because patients in Bern are followed for a shorter duration, very little discrepancy in electronically monitored adherence was found. Patients at the Lausanne and Bern centers were not blinded to using EMs because the monitors were used routinely in the respective medication adherence programs.

Reconciliation of Electronic Monitors Raw Data With Pill Count

Electronic monitor raw data were extracted using Medamigo software (AARDEX Ltd, Sion, Switzerland) where percentage of adherence was calculated as the number of openings/doses recorded by EMs over the number of prescribed doses/expected openings for a specific time period. This period is defined as the number of days elapsed between 2 consecutive patient visits at the pharmacy, ie, an intervisit patient phase. Overall adherence was calculated as the average adherence for all drugs taken. In the Lausanne center, periods of nonsystematic use of EMs, such as NMPs and periods of pocket dosing, were identified by the EMs patient visit report, and adherence based on EM data was then compared with that based on pill count data. We calculated the absolute difference between electronic adherence, as measured using EMs (I), and pill count (J) using the formula: (ABS(J-I)/J) × 100. If the difference between pill count and electronic adherence was more than 25%, periods of nonmonitoring and pocket dosing, as described by the patients before reviewing the EMs results and notification from the pharmacist in the patient visit report, were identified and the electronic adherence calculation was adjusted accordingly. If the difference was still more than 25% or periods of pocket dosing could not be identified, these were considered as missing values because EM measurements were not sufficiently reliable for research purposes.

We decided to use a 25% cutoff because we believed that a difference above that threshold was considered substantial. A "day" was defined as the 24-hour period from 3:00 am to 2:59 am for all participants to allow for those who took their ARV medication late at night. All excess EM openings (more than the number of prescribed doses/openings) were ignored. Phases in which EMs could not be read or analyzed due to technical reasons (such as when patients forgot to bring their EMs to visits or NMPs that could not be reconciled based on the visit reports) were excluded from the analysis and considered as missing values. Because patients used 1 EM per ARV drug, if only 1 EM of 2 or 3 was valid, analysis of the phase was completed using the valid data only. We performed a sensitivity analysis with the discarded data after reconciliation and compared both results.

Data Analysis

Demographic and clinical characteristics were compared between different cognitive groups using the χ^2 test, Fisher's exact test, Kruskal-Wallis test, or analysis of variance (followed by a post hoc test if necessary) where appropriate. Significance was set at a P value of less than .05 for all statistics. Variables included in the descriptive analysis were age, sex, education, ethnicity, sexual orientation, HIV transmission group, follow-up duration with EMs, treatment duration, HIV viral load, nadir CD4 count, and CD4 count at the time of neurocognitive assessment.

Repeated binary measures were available for daily EM information throughout the entire follow-up period that stated whether a patient took at least the prescribed dose of medication on any day d. On each day d, implementation, the operational definition of adherence in this study, was computed as the proportion of patients who took at least the prescribed dose at that time [9]. However, for clarity, we herein use the word "adherence", which strictly refers to implementation. Adherence was evaluated for each of the 3 groups of patients: normal (absence of NCDs), HIV-associated disorders, and non-HIV-associated disorders. Generalized estimated equations (GEE) were adopted to model adherence over time. For sufficient number of patients in each group at each date, analyses were truncated to 3 years, starting from the beginning of individual follow-up. The GEE models represent an extension of the logistic model, considering the possible dependence between repeated binary measures in the same individual. These models are based on correlation matrices that represent mean dependency between individual measurements, providing a robust estimation of the population mean response (adherence).

Adherence was modeled both globally and according to the neurocognitive group. In this case, the group variable was introduced into the model both alone, measuring the group effect at baseline, and with an interaction with time, measuring the effect of neurocognitive diagnosis on the adherence pattern over time. The latter was expressed by different powers of the time variable (polynomial model), retaining only significant time effects and interactions in the model ($P < .05$). The same statistical approach was adopted to estimate the probability of detectable ribonucleic acid (RNA) over time (RNA level above

20 copies/mL) according to the neurocognitive diagnosis. All analyses were completed using the R statistical package, version 3.1 (R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria [URL: http://www.R-project.org]).

Ethics

All patients who are involved in the SHCS, Neuro-HIV multidisciplinary outpatient clinic, or the NAMACO study have provided written consent to use their data for each of the research projects. The research proposal to use electronic medication adherence data was approved by the Ethics committees of the cantons Vaud and Bern in Switzerland, protocol number PB_2016-02022 (72/15) on August 29, 2016.

RESULTS

Descriptive Statistics

We included 59 patients: 42 from Lausanne and 17 from Bern. At the time of neurocognitive assessment, as shown in Table 1, the median (Q1, Q3) CD4 count was 603 (486–735) cells/μL; the median (Q1, Q3) age was 53 (47–58) years, and 39 subjects (66%) were male. Of 59 patients, 22 (35%) had no neurocognitive deficit, 16 (27%) had HAND (9 ANI, 4 MND, and 3 HAD), and 21 (35%) had non-HIV-related NCDs. Non-HANDs were attributed to other confounding factors such as psychiatric disorders (mild to severe depression, anxiety), substance abuse (alcohol, illicit drug or cannabis use), and cerebrovascular or neurodegenerative diseases. The median duration of follow up in the adherence program was 2.3 years, and the median time between the start of follow up in the adherence program and the date of neurocognitive assessment was 3.42 years. All patients received neurocognitive assessments during follow up in the medication adherence program, except for 2 who received their neurocognitive assessments before being followed in the adherence program. Participant groups were significantly different in terms of race/ethnicity, education, sexual orientation, duration since starting treatment, and source of HIV transmission.

Reconciliation of Electronic Monitors Data

The analysis of EMs adherence data yielded 2606 intervisit patient phases over a median of 858 days (2.3 years) of daily electronic measurements, which corresponds to 65 127 EM openings in total. Validation of the electronic EMs data from the Lausanne center showed that 35 patients over 367 phases had a difference of more than 25% between the 2 measures of adherence used, pill count, and electronic measurement by EMs, for a minimum of 1 patient phase. Over 91 phases for 24

Table 1. Patient Sociodemographic and Clinical Characteristics

Characteristics	All Patients *n* = 59	Absence of NC Disorders *n* = 22	HAND *n* = 16	Non-HAND *n* = 21	*P* Value
Age median (Q1, Q3)	53 (47, 58)	53.3 (48, 57)	51 (47, 57)	50 (42, 58)	.248
Gender					
Male	39 (66%)	17 (77%)	9 (56%)	13 (62%)	.351
Ethnicity					
White	44 (75%)	21 (95.4%)	10 (63%)	13 (62%)	.011
Sexual Orientation					
Heterosexual	41 (69%)	2 (20%)	10 (76%)	16 (76%)	.192
Source of HIV Contamination					
Heterosexual transmission	23 (39%)	3 (13.6%)	10 (62.5%)	10 (47.6%)	.006
Education					
Less than a bachelor's degree	44 (75%)	11 (50%)	15 (38%)	18 (86%)	.001
CD4 nadir	205 (119–261)	208 (131–347)	177 (106–219)	208 (91–253)	.613
CD4 cell count/μL, median (IQR) at inclusion in the adherence program	409 (242–535)	409 (219–504)	487 (278–638)	357 (275–489)	.417
HIV-RNA copies/mL, median (IQR) at inclusion in the adherence program	117 (0–36 150)	1735 (7–118 491)	79 (42–425)	100 (0–36 150)	.529
Duration of follow up with EMs during the adherence program (days, Q1, Q3)	858 (168, 1957)	191 (75, 1275)	1460 (653, 2445)	1068 (288, 2308)	.389
CD4 cell count/μL, median (IQR) at time of neurocognitive assessment	603 (486–735)	607 (500–654)	605 (474–735)	601 (498–829)	.498
Undetectable patients at time of neurocognitive assessment	48 (81%)	15 (68%)	15 (94%)	18 (85%)	.152
Difference between date of neurocognitive assessment and start of follow-up in the adherence program (days, Q1, Q3)[a]	1252 (562, 2195)	587 (373, 1894)	1364 (1116, 2340)	1450 (668, 2105)	.206
Duration of treatment (days, Q1, Q3)	3430 (1781, 5655)	2415 (1507, 4348)	2748 (820, 4837)	3511 (2931, 6265)	.041
Duration of treatment before EMs start of follow-up (days, Q1, Q3)	2124 (21, 4357)	1356 (0, 3283)	796 (25, 2413)	3116 (1898, 4907)	.077

Abbreviations: EM, electronic monitor; HAND, human immunodeficiency virus-associated neurocognitive disorders; HIV, human immunodeficiency virus; IQR, interquartile range; NC, neurocognitive; RNA, ribonucleic acid.

[a]Follow up for all patients in the adherence program began before they had their neurocognitive assessments, except for 2 who had their neurocognitive assessments before being followed in the adherence program.

patients, the difference between the 2 measures was resolved by identifying NMPs and recalculating adherence accordingly.

Adherence to Combined Antiretroviral Therapy

As shown in Figure 1, adherence over 3 years of 65 127 daily repeated electronic adherence measurements showed a significant decrease in adherence after 1 year in the group of patients diagnosed with HAND compared with the groups without a HAND diagnosis (absence of NCDs and non-HIV-associated disorders), for whom adherence remained approximately stable during the 3 years of follow-up. A GEE model of adherence as a function of time (polynomial function), HAND diagnosis (absence of NCDs/HIV-associated disorders/non-HIV-associated disorders), and their interactions showed a significant interaction of HIV-associated disorders with time, ie, a significantly different adherence pattern over time for patients diagnosed with HAND (the solid blue curve in Figure 1). In contrast, adherence in patients without NCDs and patients with non-HIV-associated disorders did not vary significantly over time (superposition of solid red and green curves in Figure 1).

Variability of the model predictions as assessed by model-derived confidence intervals (CIs) (dashed curves in Figure 1) was especially large in the case of HIV-associated disorders for the second half of follow-up period. Adherence was estimated at approximately 85% (CI, 76%–91%) at the beginning of the follow-up for all HAND categories (no significant effect of HAND variable at baseline). After 3 years, adherence slightly increased to 95% (CI, 85%–98%) in patients without NCDs and patients with non-HIV-associated disorders, but it decreased dramatically to approximately 50% (CI, 20%–80%) in HAND patients.

Sensitivity analysis (Supplementary Figure 1) showed a slightly lower estimate of adherence as presented in Figure 1. The adapted model was similar to that in the principal analysis, and the patterns of the curves were similar. Electronic monitors can underestimate adherence rates among individuals who remove their pills from EMs with the intention of ingesting them later, so-called "pocket-dosing". Therefore, these data were not included in the principal analysis and were only used in the sensitivity analysis to compare the results.

Viral Load Over Time

As shown in Figure 2, the probability of having a detectable viral load (probability of HIV RNA >20 copies/mL) varied according to the neurocognitive group (absence of NCDs, non-HIV-associated disorders, HIV-associated disorders). Patients with HAND showed an increased probability of detectable RNA relative to the other 2 categories.

DISCUSSION

This study expands on longitudinal adherence patterns to cART over a course of 3 years' time as a function of HAND diagnosis. To our knowledge, the current study is the first to

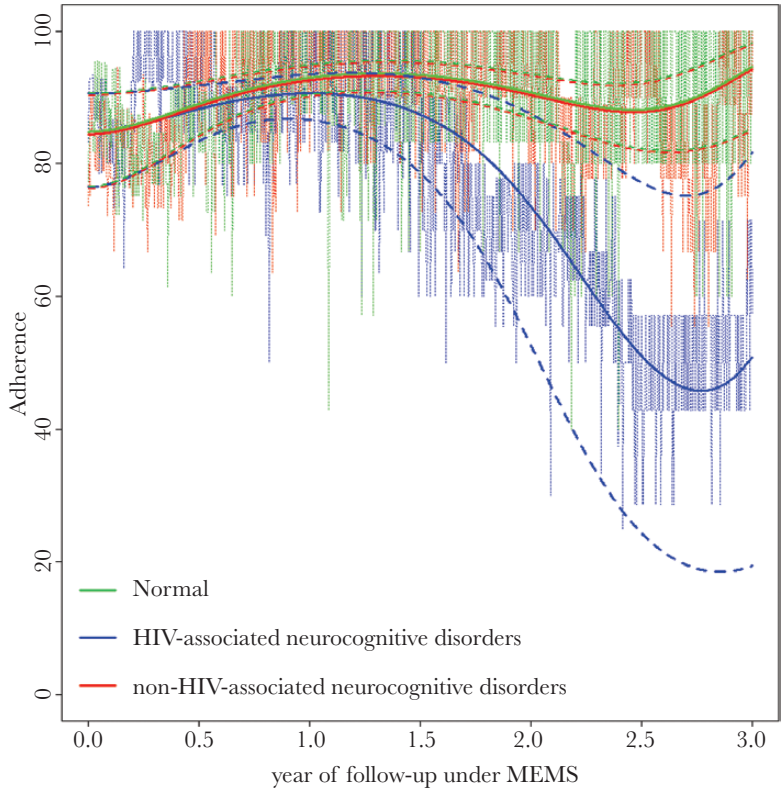

Figure 1. Adherence to cART per neurocognitive group over time. Abbreviation: HIV, human immunodeficiency virus.

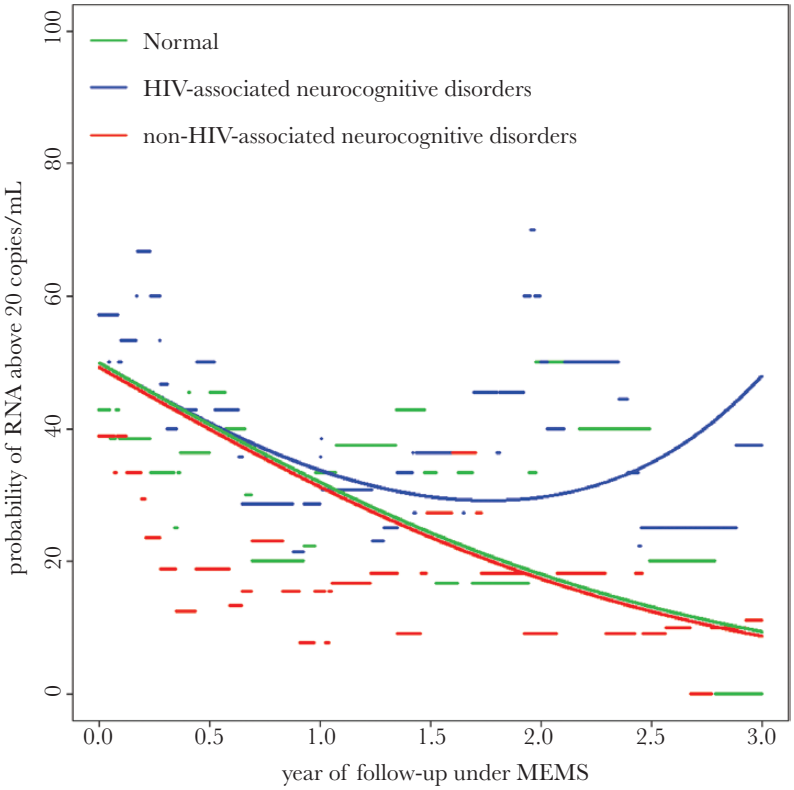

Figure 2. Human immunodeficiency virus (HIV) ribonucleic acid (RNA) detectability over time per neurocognitive group.

demonstrate EMs measured adherence as a function of neurocognitive impairment over a long period of time. Consistent with our study hypothesis, patients diagnosed with HAND had higher rates of nonadherence and steeper declines in adherence over time and a higher probability of having a detectable viral load. Indeed, HAND is typically associated with memory impairment that leads to forgetfulness, which represents a challenge for medication management in daily life [25]. Human immunodeficiency virus-associated NCD is also associated with impairment in executive functions, psychomotor slowing, and attention, all of which have been shown to have a negative impact on adherence [18, 26].

Patients with cognitive disorders not related to HIV infection exhibited a similar adherence pattern as those without neurocognitive deficits. Non-HIV-related cognitive impairments were related to depression, anxiety, alcohol, illicit drug or cannabis use, smoking, and illiteracy. It is notable that a number of HIV-positive patients suffer from depression and anxiety as a consequence of their HIV status [27, 28]. In the context of HIV infection, alcohol use, depression, and anxiety are associated with a greater risk of nonadherence [29, 30]. Figure 1 shows that patients diagnosed with HAND exhibited lower adherence than those with NCDs not related to HIV. This shows that the association between HAND and adherence is stronger than non-HIV-related conditions. Furthermore, patients with adherence difficulties, or those initiating cART treatment, are those who are referred to the adherence program. Our results show that patients with adherence difficulties and no HAND still show higher adherence than those who have HANDs.

As similarly reported in previous studies [1], although patients diagnosed with HAND did not have any detectable viremia at the time of neurocognitive assessment, they nevertheless demonstrated neurocognitive deficits. However, as shown in Figure 2, the probability of obtaining detectable virological rebound was higher in the group with HIV-associated disorders than in the groups having non-HIV-associated disorders and those without NCDs.

Strengths and Limitations

Because medication adherence of patients was followed for a median of 3.4 years before the date of neurocognitive assessment, which was only cross-sectional in time, we were unable to establish a temporal causality between declines in cognition and suboptimal adherence. Thus, only an association can be proposed. In addition, because NCD testing is not performed on a routine basis from HIV baseline diagnoses over time, it may be possible that those patients presented with NCDs years before the time of neurocognitive assessment. Patients could have intentionally or nonintentionally become nonadherent and consequently developed neurocognitive problems or, conversely, may have developed nonadherence as a consequence of their NCDs, especially in the case of prospective memory and

attention disorders. Nevertheless, our analysis showed that the probability of having a detectable viral load over time (>20 copies/mL) was higher among the group with HANDs compared to the other 2 groups (Figure 2).

Another limitation of our study is the small number of participants, which did not allow us to analyze the different patterns of nonadherence according to the severity of the NCDs (ANI, MND, and HAD). Despite being asymptomatic, patients diagnosed with ANI are clinically relevant because the literature shows that both symptomatic and asymptomatic NCDs are associated with lower adherence, lower quality of life, and unemployment [31]. In addition, patients with ANI can transition to more severe forms of HAND [32]. However, despite the small sample size, we were able to show significant patterns of adherence among the 3 groups (HANDs, non-HAND, and absence of NCDs). This represents a valuable combination of data collected prospectively by the SHCS, a medication adherence program in which EMs are used routinely in care in addition to standardized neurocognitive assessments. Moreover, we analyzed daily electronic measurements of adherence over the entire duration of follow up, with a median of 858 days (2.3 years); thus, although the analysis was performed in 59 patients, the data representing daily measurements provided in-depth daily and continuous representations of patient behavior over an extended period of time. This allowed us to demonstrate the exact long-term patterns of chronic medication intake among HIV-positive patients instead of a summary of adherence measurements or self-reported adherence, which can introduce bias. In conclusion, there appears to be an association between HAND and medication adherence. Further research with several neurocognitive tests performed over time, along with medication adherence monitoring with EMs, is needed to further investigate the evolution of adherence over time as a function of the presence or absence of NCDs.

CONCLUSIONS

Our results indicate that the detection of a NCD should raise concern that the patient may be at higher risk of viral load detection and virologic failure. Furthermore, for patients presenting an increase in viral load, assessing their cognitive function could be appropriate if the decrease in adherence is nonintentional and linked to cognitive disorders. To date, the most successful interventions for preventing, delaying, or improving HAND include early initiation of and adherence to cART [33]. Therefore, developing effective strategies to enhance medication adherence in these patients is crucial. The key to developing effective strategies is knowledge of a patient's pattern of drug-taking behavior, and analyses of EMs data can provide this information. Combining drug-taking behavior with patients' daily routines (eg, with meals or at bedtime) or relying on support from significant others and inviting them to a medication adherence support program are good examples of strategies that could be developed to help patients diagnosed with HAND overcome their nonadherence.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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