Human Immunodeficiency Virus-associated Neurocognitive Impairment in Diverse Resource-limited Settings

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Background. Neurocognitive impairment remains a common complication of human immunodeficiency virus (HIV) despite effective antiretroviral therapy (ART). We previously reported improved neurocognitive functioning with ART initiation in 7 resource-limited countries for HIV+ participants from the AIDS Clinical Trials Group (ACTG) 5199 International Neurological Study (INS). Here, we apply normative data from the International Neurocognitive Normative Study (INNS) to INS to provide previously unknown rates of neurocognitive impairment.

Methods. The A5199 INS assessed neurocognitive and neurological performance within a randomized clinical trial with 3 arms containing World Health Organization first-line recommended ART regimens (ACTG 5175; PEARLS). The ACTG 5271 INNS collected normative comparison data on 2400 high-risk HIV-negative participants from 10 voluntary counseling and testing sites aligned with INS. Normative comparison data were used to create impairment ratings for HIV+ participants in INS; associations were estimated using generalized estimating equations.

Results. Among 860 HIV+ adults enrolled in ACTG 5199, 55% had no neurocognitive impairment at baseline. Mild neurocognitive impairment was found in 25%, moderate in 17%, and severe in 3% of participants. With the initiation of ART, the estimated odds of impairment were reduced 12% (95% confidence interval, 9%, 14%) for every 24 weeks ($P < .0001$) on ART. Mild impairment dropped slightly and then remained at about 18% out to week 168.

Conclusions. Almost half of HIV+ participants had neurocognitive impairment at baseline before ART, based on local norms. With ART initiation, there were significant overall reductions in neurocognitive impairment over time, especially in those with moderate and severe impairments.

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Keywords. HIV-associated neurocognitive disorders; antiretroviral; international settings; neurology; neurocognitive.

In a metastudy of large, randomized, controlled trials in human immunodeficiency virus (HIV), we previously demonstrated that mild neurocognitive impairment and HIV-associated neurocognitive disorders (HAND [1]) continue in persons on stable antiretroviral treatment (ART) in the United States [2].

The overwhelming majority of persons with HIV are living in resource-limited settings (RLS [3]). There is a lack of infrastructure and expertise for conducting neurological and neuropsychological research and clinical care in these settings, with many having a complete lack of capacity to conduct neuropsychological assessments [4]. In our prior work (International Neurological Study [INS] AIDS Clinical Trials Group [ACTG] 5199), our group established the infrastructure and training necessary to conduct a neurological clinical trial to study the effect of different first-line ART regimens in RLS. The INS documented substantial improvement in neurocognitive performance with ART initiation regardless of World Health Organization (WHO)-recommended ART regimen [5, 6].

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While the INS demonstrated the efficacy of ART in addressing neurocognitive performance, no normative data were available to put neurocognitive test performances in a clinical context (eg, normal vs impaired). The availability of normative data would also support routine assessment, clinical interpretation, and diagnosis for many other neurological and learning disorders in RLS. To provide that capability, the International Neurocognitive Normative Study (INNS, ACTG 5271 [7]) was designed and conducted.

There are major unresolved concerns regarding the impact of HIV on the nervous system addressed here, including whether neurocognitive impairment continues despite viral suppression with effective ART and the prevalence and incidence of neurocognitive impairment in RLS with HIV subtypes other than subtype B (which predominates in Western and high-income countries). Through the application of INNS normative data to the INS neurocognitive data, we provide the prevalence of neurocognitive impairment prior to ART and the course of neurocognitive impairment following the initiation of effective ART over time in RLS.

METHODS

Here, we briefly highlight the methods, as the study methods have been detailed in prior publications [6, 7].

ART-naïve participants with CD4+ cell counts <300 were enrolled in ACTG PEARLS (A5175) and randomly assigned to start 1 of 3 WHO-recommended first-line antiretroviral regimens: efavirenz (EFV)/lamivudine (3TC)/zidovudine (ZDV), emtricitabine (FTC)/atazanavir (ATV)/didanosine enteric-coated (ddI-EC), or EFV/FTC/tenofovir (TDF). Enrollment criteria excluded any condition that would compromise the person's ability to participate in the study, adhere to study requirements, or confound the analysis of the results, including acute illness and psychiatric conditions. The INS substudy enrolled 860 of these participants in Rio de Janeiro and Porto Alegre, Brazil (n = 161); Chennai and Pune, India (n = 184); Blantyre and Lilongwe, Malawi (n = 133); Johannesburg and Durban, South Africa (n = 167); Lima, Peru (n = 62); Chiang Mai, Thailand (n = 73); and Harare, Zimbabwe (n = 80). Participants were then followed on ART every 6 months for up to 192 weeks with neurocognitive and neurological assessments (from February 2006 to May 2010). Participants who failed the first-line treatment and were switched to alternative regimens (ie, step 2 and step 3 of the study) were not included in this analysis.

For INNS (A5271), 2400 participants were stratified by site/country (240 per site) and 8 levels of relevant demographics: age (above and below 35 years), sex (male/female), and education (above and below 10 years). Participants who had tested HIV negative within 30 days were recruited from voluntary counseling and HIV testing sites that were aligned with the same sites as INS. Participants were enrolled in the study beginning in February 2011, and the study was closed in October 2013. The eligibility criteria mirrored those of INS, including the exclusion

of any active severe psychiatric illness, active drug abuse, or hospitalization within 14 days. The neurocognitive battery for INS included timed gait, grooved pegboard, finger tapping, and semantic verbal fluency. The INNS neurocognitive battery augmented the existing INS battery with the additional tests of the Hopkins Verbal Learning Test–revised, Color Trails 1 and 2, Digit Symbol, the International HIV Dementia Scale, and the Activities of Daily Living Scale. Here, we report impairment for the INS test battery and participants. Visits were conducted at each study site to provide training and quality assurance on as close to an annual basis as possible by the primary investigator (K. R. R.) and neurologist (C. D. H.). Additional training, quality assurance, and certifications were conducted centrally in Washington, D.C., on an annual basis. Formal HAND diagnoses were not available as INS was conceived and conducted prior to the diagnostic nomenclature revision [1]. We applied the neurocognitive normative data collected in INNS to INS in order to derive neurocognitive impairment estimates. A5199 neuropsychological test scores were transformed to *z* scores using A5271 normative data (ie, means and standard deviations [SDs] within demographic stratum and country). The formula used within country/stratum was $z \text{ score} = (\text{raw score} - \text{mean}) / \text{SD}$ for semantic verbal fluency and finger tapping or $z = (\text{mean} - \text{raw score}) / \text{SD}$ for grooved pegboard and timed gait.

Consistent with the neurocognitive aspects of the HAND diagnosis, impairment was assigned in the following manner: normal (no more than 1 test that falls 1 SD below the INNS normative sample mean); mild (2 tests that fall 1 SD below the INNS mean or 1 test that falls 2 SDs below); moderate (3 to 4 tests that fall 1 SD below the INNS mean or 2 tests that fall 2 SDs below); and severe (5 or more tests that fall 1 SD below the INNS mean or 3 or more tests that fall 2 SDs below). Linear and logistic regression models using generalized estimating equations with an autoregressive correlation structure (for within-patient correlation) were constructed to assess the treatment effects and country effects on neuropsychological test scores and impairment ratings. The covariates that were included in the models are country, randomized ART from A5175, baseline HIV-1 RNA stratum, screening CD4 count, baseline *z* score/impairment rating, age, sex, years of education, and week. The reference groups for sex, baseline HIV-1 RNA stratum, country, and treatment were as follows: female, >100 000 c/mL, Thailand, and treatment A. Several data unit changes were utilized in modeling, including age/10, CD4/50, and years of education/4. Thus, resulting parameters can be interpreted for a 10-year change in age, a 50-unit change in CD4 count, and a 4-year change in education. Additional sensitivity analyses were utilized to address the effects of dropout and practice/learning effect over time.

RESULTS

For a detailed description of the demographics and baseline characteristics, please refer to the primary INS and INNS

Figure 1. Change in prevalence of neurocognitive impairment following treatment initiation. Abbreviations: ART, antiretroviral therapy.

publications [6, 7]. There were no differences between the antiretroviral treatment arms with regards to neurocognitive impairment. As expected, there were differences between countries in overall neurocognitive performance ($P < .0001$), which were accounted for in the models. When applying the INNS site-specific HIV seronegative normative comparison data to create neurocognitive z scores for the INS participants, we found that 55% of ART-naïve individuals with CD4+ cell counts <300 had normal neurocognitive performance. Of the 387 participants impaired, 55.3% had mild impairment, 37.2% had moderate impairment, and 7.5% had severe impairment (Figure 1).

After ART initiation, neurocognitive impairment was substantially reduced, with 37% impaired at week 24, 36% impaired at week 48, 31% at week 72, 27% at week 96, 26% at week 120, 29% at week 144, 26% at week 168, and 20% at week 192 (Table 1). ART reduced neurocognitive impairment from baseline by 12% (95% confidence interval, 9%, 14%) for every 24

weeks on ART ($P < .0001$). Neurocognitive performance improvement on ART was also sustained over time (Figure 2). The percentage of participants in the normal range of neurocognitive performance improved from 55% at baseline to 74% among those completing week 168 (Figure 1). As for severity of impairment, there were reductions in moderate and severe impairment with longer duration of antiretroviral treatment. At week 168, those with moderate neurocognitive impairment reduced to 6% and severe neurocognitive impairment to 0.4%. Mild neurocognitive performance impairment dropped only slightly, however, and then remained at about 19% out to week 168.

In terms of incidence of impairment on study, the on-study impairment rate was calculated from baseline to last visit on study. The majority of participants remained stable (56.46%) or improved (33.41%), while only 10.12% had new onset of impairment (Table 2, Figure 3). To address potential learning or practice effects during the initial study, the incidence of impairment

Table 1. Summary of Impairment Ratings Over Time

Neurocognitive Impairment by Week										
Impairment	Week									
Frequency, Column Percent (%)	0	24	48	72	96	120	144	168	192	216
Normal	466 (54.63)	513 (63.49)	479 (64.12)	462 (68.75)	394 (72.56)	359 (74.33)	335 (70.63)	310 (73.99)	220 (80.00)	43 (82.69)
Mild	214 (25.08)	179 (22.15)	164 (21.95)	139 (20.68)	101 (18.60)	91 (18.84)	96 (20.21)	81 (19.33)	44 (16.00)	8 (15.39)
Moderate	144 (16.88)	103 (12.74)	95 (12.72)	65 (9.67)	46 (8.47)	31 (6.31)	42 (8.84)	26 (6.21)	9 (3.27)	0 (0.00)
Severe	29 (3.39)	13 (1.60)	9 (1.20)	6 (0.89)	2 (0.37)	2 (0.41)	2 (0.42)	2 (0.48)	2 (0.73)	1 (1.92)
Total n evaluated	853	808	747	672	543	483	475	419	275	52
Missing ^a	7 (0.81)	19 (2.30)	31 (3.98)	15 (2.18)	10 (1.81)	8 (1.63)	10 (2.06)	13 (3.01)	6 (2.14)	1 (1.89)
Total n ^a	860	827	778	687	553	491	485	432	281	53

^aMissing means missing values while on study.

Figure 2. Estimated neurocognitive impairment over time. Abbreviations: ART, antiretroviral therapy.

ratings from week 48 to week 168 was calculated. Almost all learning/practice effect occurs within the first 3 assessments (0, 24, and 48 weeks), and we have previously used this method to address learning effects [8]. From week 48 to week 168, 69.49% of the participants remained stable, 20.10% improved, and 10.39% declined. Additional analyses were undertaken to assess the effect of dropout by demonstrating the incidence of impairment in the participants who fulfilled all of the visits from baseline until week 168. Analyses indicated that dropout did not account for improvement seen on study follow-up, as the incidence for this group from baseline to week 168 also mostly remained stable (56.01%) or improved (34.13%), with the minority showing declined impairment (9.85%).

DISCUSSION

INS was the first multinational antiretroviral randomized clinical trial to address HIV-associated neurocognitive dysfunction in RLS [5]. Here, we applied the site-specific normative

comparison data collected in INNS to assess the prevalence of neurocognitive impairment in RLS [6]. We found a substantial prevalence of neurocognitive impairment at baseline in HIV+ ART-naïve participants with CD4+ cell counts <300 in diverse RLS. The prevalence of neurocognitive impairment was very consistent with estimates of neurocognitive impairment and HAND in previous large US studies [2, 9].

With ART initiation in INS, there were significant overall reductions in neurocognitive impairment over time, especially in those with moderate and severe impairments. There were fewer reductions in mild neurocognitive impairment, suggesting that other mechanisms could be driving this impairment, including legacy effects of past neuronal injury/cell death prior to ART and/or ongoing inflammation despite viral suppression. The incidence rating from baseline to the end of the study showed that a third of the impaired participants showed improvement at the last visit.

The observed changes in neurocognitive performance after ART initiation likely reflect several factors. ART initiation has consistently shown neurocognitive improvements in those naïve to or failing treatment [10, 11]. In part, this improvement is related to entrance to care, learning or practice effects, in addition to direct benefit of reducing HIV RNA viral load. Lower screening RNA stratum was related to better performance over time in grooved pegboard dominance, with similar trends for grooved pegboard nondominance, verbal fluency, and timed gait ($P < .15$) [6]. However, the improvement is not solely due to initial practice or learning effects since there was additional improvement following the first 3 visits. Dropout did not account for improvement since the incidence rates among participants attending every visit from baseline to week 168 were similar to

Table 2. Estimated Incidence of Neurocognitive Impairment

Change	Change in Neurocognitive Function (%)		
	On Study ^a	Accounting for Dropout ^b (Complete Cases Only)	Accounting for Learning and Practice Effect ^c
Stable	56.46	56.01	69.49
Improvement	33.41	34.13	20.10
Decline	10.21	9.85	10.39

^aOn study calculated from baseline to last visit.

^bAccounting for dropout calculated from baseline to visit at week 168 for the participants who attended all of the study visits.

^cAccounting for learning and practice effect calculated from the third visit (week 48) to visit at week 168.

There was substantial improvement in neurocognitive performance and lower incidence of impairment from first to last visit.

Figure 3. Incidence of neurocognitive impairment and improvement on study from baseline to last visit.

those of the larger evaluable cohort. There were no observed differences in the 3 ART regimens in reducing impairment; effective ART led to improved neurocognitive outcomes regardless of ART regimen.

Limitations of this study could be associated with the selection criteria of the HIV+ participants, who were enrolled from a larger clinical trial that recruited individuals who would be compliant with study procedures over an extended period. This could have led to a healthier cohort with fewer neurological complications. The inclusion criterion of at least a Karnofsky score of 70 infers that participants were already less likely to have neurological abnormalities. Another limitation could be the time lag in collecting the normative data. Collection of the normative data in INNS began 8 months after the close of the INS study. The clinical staff was trained by the same principle investigators, but there was a gap of about 5 years between baseline assessments. Last, the neuropsychological battery was brief, but it was chosen for the INS and INNS study based on prior experience in clinical trial and cohort studies in the ACTG and then augmented with additional tests to meet minimal HAND Frascati criteria. Maintenance of a short battery with the least language- and culture-specific items made it possible to easily implement and sustain the study in diverse RLS [6, 7].

As has been documented in other large, randomized, controlled trials [2] and observational studies [12], we observed

that there is a residual mild neurocognitive impairment unaddressed by ART. Recent findings have shown that even with long-term suppressive ART for a median of 8.5 years, almost half of cells in cerebrospinal fluid (CSF) have detectable HIV DNA [13]. Detectable HIV DNA in CSF in this cohort was also associated with neurocognitive impairment, suggesting a functional consequence to latent HIV [13]. There is strong evidence that presymptomatic neurocognitive impairment is a precursor to progression to symptomatic HIV-associated neurocognitive disorders [14]. Whether ART agents that act through different mechanisms such as C chemokine receptor type 5 inhibitors or integrase inhibitors may further address very low-level HIV replication in the central nervous system (CNS) and reduce this lingering impairment remains to be fully investigated. Ongoing inflammation in the presence of latently infected but dormant cells in the absence of CNS HIV replication may also be responsible for the residual mild impairment. Strategies to reduce the latent reservoir and compartmentalized virus in the CNS will be more difficult to achieve due to the protective blood–brain barrier. Adjunctive antiinflammatory agents may be effective in addressing the residual mild impairment if ongoing inflammation is found to be the primary underlying mechanism behind the mild impairments seen on stable ART.

In summary, this study documented that almost half of those living with nonsubtype B HIV in RLS had neurocognitive

impairment and that effective ART in RLS led to reductions in that neurocognitive impairment. These improvements in neurocognitive performance would likely lead to sustained improvements in productivity and quality of life in those living with HIV in RLS.

Notes

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