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A Multinational Study of Neurological Performance in Antiretroviral Therapy-Naïve HIV-1-Infected Persons in Diverse Resource-Constrained Settings

K Robertson[1], **J Kumwenda**[2], **K Supparatpinyo**[3], **H Jiang**[4], **S Evans**[4], **TB Campbell**[5], **RW Price**[6], **R Murphy**[7], **C Hall**[1], **CM Marra**[8], **C Marcus**[1], **B Berzins**[7], **R Masih**[9], **B Santos**[10], **MT Silva**[11], **N Kumarasamy**[12], **A Walawander**[13], **A Nair**[13], **S Tripathy**[14], **C Kanyama**[15], **M Hosseinipour**[15], **S Montano**[16], **A La Rosa**[16], **F Amod**[17], **I Sanne**[18], **C Firnhaber**[18], **J Hakim**[19], **P Brouwers**[20], and **the AIDS Clinical Trials Group**

[1]UNC, Chapel Hill, NC, US [2]Queen Elizabeth, Blantyre, Malawi [3]Chiang Mai University, Chiang Mai, Thailand [4]Harvard University, Boston, MA, US [5]University of Colorado Denver, Aurora, CO, US [6]University of California San Francisco [7]Northwestern University, Chicago, IL [8]University of Washington, Seattle, WA [9]Social & Scientific Systems, Inc [10]Porto Alegre, Brazil [11]Fiocruz, Rio De Janeiro, Brazil [12]Chennai, India [13]Frontier Science & Technology Research Foundation, Buffalo, NY [14]Pune, India [15]Lilongwe, Malawi [16]Lima, Peru [17]Durban South Africa [18]Johannesburg, South Africa [19]Harare, Zimbabwe [20]National Institute of Mental Health

Abstract

Background—Little is known about how the prevalence and incidence of neurological disease in HIV-infected patients in resource-limited settings. We present an analysis of neurological and neurocognitive function in antiretroviral naïve individuals in multinational resource-limited settings.

Methods—This prospective multinational cohort study, a substudy of a large international randomized antiretroviral treatment trial, was conducted in 7 low and middle income countries in Sub-Saharan Africa, South America, and Asia. Subjects were HIV-infected and met regional criteria to initiate antiretroviral therapy. Standardized neurological examination and a brief motor-based neuropsychological examination were administered.

Results—860 subjects were studied. Overall 249 (29%) had one or more abnormalities on neurological examinations, but there was a low prevalence of HIV-associated dementia (HAD) and minor neurocognitive disorder (MND). Twenty percent of subjects had evidence of peripheral neuropathy. There were significant differences across countries ($p<.001$) in neuropsychological test performance.

Conclusions—In this first multinational study of neurological function in antiretroviral naïve individuals in resource-limited settings, there was a substantial prevalence of peripheral neuropathy and low prevalence of dementia and other CNS diseases. There was significant variation in neurocognitive test performance and neurological examination findings across

Address correspondence and reprint requests to Dr. Kevin R. Robertson, Department of Neurology, University of North Carolina, 2128 Physician Office Building, 170 Manning Drive, Chapel Hill, NC 27599-7025, USA. kevinr@neurology.unc.edu.

*note: The authors wish to dedicate this manuscript to Dr. Jens Mielke, who died during the conduct of the study. He is missed by all who knew him.

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countries. These may reflect cultural differences, differences in HIV-related and unrelated diseases, and variations in test administration across sites. Longitudinal follow-up after antiretroviral treatment initiation may help to define more broadly the role of HIV in these differences as well as the impact of treatment on performance.

Keywords

HIV; resource-limited; cognitive impairment; CNS; neuropsychological examination

Introduction

The burden of the human immunodeficiency virus type 1 (HIV-1) epidemic is staggering, particularly in resource-poor, developing parts of the world where 95 percent of new infections occur (World Health Organization 2003). Since the early years of the HIV-1 epidemic in the developed world, it has been recognized that the central and peripheral nervous systems (CNS and PNS) are impacted in HIV-1 infection, both by opportunistic infections and by conditions that relate to the virus, itself. Though the precise mechanisms are uncertain, there is considerable evidence to suggest that the local effects of viral and immune factors in the CNS and PNS underlie this neurotoxicity (Price and Spudich 2008).

The spectrum of HIV-related CNS diseases has recently been given the name HIV-Associated Neurological Disorders (HAND) (Antinori et al. 2007). This includes not only the more severe form of HIV-associated dementia (HAD), but also less severe nervous system dysfunction, termed HIV-associated minor neurocognitive disorder (MND), that is detected in a larger portion of infected patients. These disorders were previously known as acquired immunodeficiency syndrome (AIDS) Dementia Complex and minor cognitive/motor disorder respectively (Navia et al. 1986; Navia et al. 1986; American Academy of Neurology 1991; Robertson and Hall 1992; McArthur et al. 1993). In the era prior to highly active antiretroviral therapy (HAART), as many as 80% of people who died from AIDS in the United States had autopsy evidence of CNS injury attributable to HIV-1 regardless of whether there had been clear manifestations of HAD during life (Elder and Sever 1988). Likewise, the PNS is commonly affected in HIV-1 infection, and while a variety of different neuropathies have been described, the predominant type is a distal primary sensory polyneuropathy (DSPN) that is often associated with severe pain and reduction in quality of life. DSPN has been reported to have a prevalence of up to 60% in advanced HIV-1 disease (Simpson et al. 2006). A complicating factor is that the deoxynucleotide antiretroviral drugs, including, didanosine, zalcitabine, and stavudine may cause a neuropathy that is clinically indistinguishable from DSPN (Sacktor 2002; Schifitto et al. 2005).

The burden of neurological disease on families and communities is substantial, with loss of productivity and income for the diagnosed and for those who take the primary responsibility as caretakers. In resource-limited settings with high rates of HIV-1 infection the toll is likely devastating, but remains to be documented (Schifitto et al. 2001; Tozzi et al. 2004). In the developed world, cognitive impairment is relatively common in HIV-infected individuals who have not been treated with antiretroviral therapy (McArthur et al. 1993). Little is known about the prevalence of HAD, milder neuropsychological dysfunction and peripheral neuropathy in HIV-1 infected people in resource-limited settings who have not received ART. The overall purpose of our study was to conduct neurological and neuropsychological assessments in treatment-naïve HIV-1-infected individuals in order to determine HAND and peripheral neuropathy prevalence in those initiating treatment, and, eventually, the impact of different regimens on these conditions. We report here the baseline pre-antiretroviral treatment results from ACTG 5199.

Methods

Sites

A5199 was an AIDS Clinical Trials Group (ACTG) study that was organized as a substudy of ACTG A5175, a randomized trial that focused on treatment strategies and systemic disease outcomes. The international ACTG sites that participated in the study were located in Rio de Janeiro, Brazil; Porto Alegre, Brazil; Chennai, India; Pune, India; Blantyre, Malawi; Lilongwe, Malawi; Lima, Peru; Johannesburg, South Africa; Durban, South Africa; Chiang Mai, Thailand; and Harare, Zimbabwe.

Procedures

Human subjects study review and approval by local and country specific review boards were obtained at each site prior to study initiation. The National Institutes for Health (NIH), National Institute for Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), and Multinational Data Safety and Monitoring Board monitored the study at intervals to ensure safe and appropriate conduct. Each international site was required to enroll 10 participants successfully in the parent study (ACTG A5175), pass a quality assurance visit, and then enroll another 10 participants successfully in A5175 before the sites were allowed to start enrollment unencumbered. This ensured that the study infrastructure was working appropriately and assured quality data collection. Once the neurological and neuropsychological exams were finalized, case report forms were developed with appropriate skip logic. Sites then translated the forms into local languages and back translated, with discrepancies resolved. Standardized training on administration of the neurological and neuropsychological examinations was conducted on site. Centralized training occurred on a biannual basis at A5199 team meetings. Sites were also provided with web-based and DVD training modules. Computerized data entry screens were implemented at the sites with infrastructure support. Rigorous data monitoring at data entry through computerized range checks, with follow-up data cleaning through multiple queries and replies were conducted throughout the study. Implausible values were queried and confirmed or corrected at intervals.

Participants

Participants were a subset of relatively healthy, HIV-1 seropositive, antiretroviral naïve individuals with CD4+ cell counts less than 300 cells/mm^3 who planned to enroll in ACTG A5175, a randomized antiretroviral treatment trial. Eligible subjects were men and women 18 years or older who had documented HIV-1 infection, CD4+ lymphocytes less than 300 cells/ mm^{-3}, Karnofsky performance score greater than or equal to 70, and no more than seven days of cumulative prior antiretroviral therapy prior to study entry. Women of reproductive potential could not be pregnant and, if participating in sexual activity that could lead to pregnancy, had to agree to the use of contraception. Persons with serious chronic, acute, or recurrent infections must have completed at least 14 days of therapy or be clinically stable. Exclusionary criteria included absolute neutrophil count less than 750 cells/ mm^{-3}, hemoglobin less than 7.5 g/dL, platelet count less than 50,000 mm^{-3}, calculated creatinine clearance less than 60 mL/min, aspartate transaminase (AST) alanine transaminase (ALT) or alkaline phosphatase greater than 5-fold above the upper limit or normal, total bilirubin greater than 2.5-fold above the upper limit of normal, clinical pancreatitis within 3 years, bradycardia (<40 min^{-1}) or a history of untreated active 2nd or 3rd degree heart block. In addition, participants were also excluded from participation in the study if they had any active severe psychiatric illness, active drug or alcohol abuse or dependence, serious illness and/or hospitalization, or any other condition that, in the opinion of the site investigator, would compromise the person's ability to participate in the study,

adhere to study requirements, or confound the analysis or interpretation of the results of the study.

Neurological and neuropsychological examinations

The A5199 neurological examination was initially developed and field-tested at selected sites. Revisions to content and length were made, eliminating confusing or culturally inappropriate items, and the examination field-tested again. The examination included a neurological history and symptom review and brief cognitive, motor, sensory and reflex assessments. Based on examination results, a neurologic diagnosis was assigned. Using the results from the neurological history and exam, the evaluator then made a judgment as to whether the neurological examination was normal or abnormal. If abnormal, the evaluator assessed the degree of abnormality and whether it appeared due to diffuse or focal central nervous system (CNS) disease, peripheral nervous system (PNS) disease or a combination.

Neuropsychological assessment is sensitive and specific for HIV-1-related cognitive dysfunction (Price and Sidtis 1990; Sidtis et al. 1993). The neuropsychological test battery was chosen based on prior experience in clinical trial and cohort studies in the United States, with particular care taken to keep the battery short and minimizing language- and cultural-specific items. The tests administered were Timed Gait, Grooved Pegboard (dominant and nondominant hands), Finger Tapping (dominant and nondominant hands), and Semantic Verbal Fluency. The neuropsychological tests were not used for assigning impairment ratings or for diagnoses of HAND in this study, as appropriate normative data does not exist to make these comparisons. Each patient was used as their own control, and comparison of the neuropsychological treatment response over time was the main outcome.

A study-specific diagnosis form was completed for each participant and included HIV-associated dementia, mild cognitive motor disorder and peripheral neuropathy, in addition to CNS opportunistic infections. In absence of appropriate normative data for the neuropsychological tests, the neurological exam summary assessment of diffuse CNS disease related to HIV of subclinical/equivocal was use coded for MND, and the mild, moderate or severe ratings were coded as HAD.

Results

Demographics

The total enrollment was 860 participants: 452 (53%) females and 408 (47%) males. The median age was 34 years, and the median educational level was 10 years (Q1-7, Q3-12). Few participants (13/860; 1.5%) had a history of intravenous (IV) substance abuse. The A5199 cohort was representative of the A5175 cohort at sites that were enrolling subjects into A5199. Table 1 presents screening CD4+ cell counts and entry HIV RNA by country.

Neurological evaluation

Overall, 249 (29%, 95% CI) of subjects had an abnormal neurological examination and the number of participants with any neurological abnormality assessment varied from 8% in Peru to 74% in Thailand (Table 2, $p<0.001$). The most common neurological diagnosis was peripheral neuropathy, diagnosed in 178 (20%, 95% CI) of subjects (Table 2). As with the other neurological diagnoses identified in this study, most neuropathy diagnoses were categorized as subclinical or mild in severity.

Only 4 participants were diagnosed with HAD (Table 3). Mild neurocognitive disorder (MND) was diagnosed in 6% of the participants with 95% CI (4.4%, 7.7%), ranging from 0% in Thailand to 14% in Zimbabwe. Substantial country variation was noted with respect

to overall neurological assessment. The percentage of participants with a normal overall neurological assessment ranged from 26% in Thailand to 92% in Peru (Table 2). Examination of the components revealed country variation in all neurological diagnoses (ranging from 1% in Malawi to 74% in Thailand) and peripheral neuropathy (ranging from 2% in India to 70% in Thailand) although most disease was scored as 'equivocal/ subclinical.' Significant variations in the frequency of HAD ($p = 0.014$) and MND ($p < 0.001$) between countries were noted. There was no significant variation on the neurological exam across HIV RNA strata (<100,000 and >100,000 cp/ml). There was a significant increase in abnormality in the overall neurologic assessment ($p = 0.009$), and HAD ($p = 0.014$) as CD4+ cell counts decreased across strata (<50, 50-99, 100-199, 200-249, and 250-299 cells/mm^3). There was no association with plasma HIV RNA level.

At baseline, as shown in Table 4, 27 (3.1%) subjects were diagnosed with peripheral neuropathy, 13 (1.5%) with extra-pulmonary tuberculosis, 37 (4.3%) with pulmonary tuberculosis, 8 (0.9%) with varicella zoster, and 11 (1.3%) with depression. Few other diagnoses were noted. Considerable country variation was noted with respect to these diagnoses. Among the 11 subjects with depression, 3 were from Brazil, 1 from India, 5 from South Africa, and 2 from Thailand.

Neuropsychological test results

The neuropsychological test baseline results are presented in Table 5. There were no significant differences in neuropsychological test performance between subjects in the two plasma HIV RNA strata noted above. Timed Gait had a mean of 12. 9 seconds (SD 2.4). Grooved Pegboard dominant hand had a mean 81.9 seconds (SD 28.1); the nondominant had a mean of 90.5 seconds (SD 29.6). Semantic Verbal Fluency had a mean of 16.2 words (SD 5.9). Fingertapping dominant had a mean of 38.3 taps (11.9); fingertapping nondominant had a mean of 35.7 taps (SD 10.4). Likewise, there were no differences in test performance in the CD4 strata (see above) except for better semantic verbal fluency scores with increased peripheral blood CD4 cell counts ($p = 0.027$). Given the number of comparisons, these results should be interpreted cautiously.

There were significant differences between countries as expected. For grooved pegboard dominant and nondominant, Malawi and Zimbabwe had slower times relative to Thailand and Peru. Similarly, the number of words recorded for semantic verbal fluency were greater for Thailand and Peru, and relatively lower for Malawi, Zimbabwe and India. South Africa, Thailand, and Peru had relatively faster timed gait scores than Malawi and Brazil. Fingertapping dominant and nondominant scores were lower in Malawi and Peru, relative to Zimbabwe and Thailand.

There were no significant relationships between plasma HIV RNA concentrations and CD4+ cell counts and performance on any of the neuropsychological tests. Compared to subjects without HAD and MND, those given a diagnosis of HAD or MND had significantly poorer performance on grooved pegboard dominant ($p < .001$), grooved pegboard non-dominant ($p < .001$), semantic verbal fluency ($p < .001$), timed gait ($p < .001$), fingertapping dominant ($p < .05$) and finger-tapping non-dominant ($p < .005$). These associations support the accuracy of the clinical diagnoses that were made without considering the neuropsychological test scores.

Discussion

The prevalence of neurological and cognitive impairment in HIV-infected individuals in the developing world has not been clearly delineated. While several studies have documented substantial prevalence of peripheral neuropathy in resource-limited settings, ranging from 11-34%, particularly among patients who had received stavudine (Grey and Berger 2007;

Affandi et al. 2008; Kumarasamy et al. 2008; Wright et al. 2008), reports of the prevalence of cognitive impairment are more variable. The prevalence of HAD in sub-Saharan Africa has been reported to be as low as 3% (Belec et al. 1989) to as high as 54% (Howlett et al. 1989). The largest study of HIV-associated neurological and cognitive impairment was performed by the World Health Organization (Maj et al. 1994). Six hundred two HIV-infected and 353 HIV-uninfected individuals were studied in Bangkok, Thailand; Kinshasa, Zaire; Nairobi, Kenya; and São Paolo, Brazil. Substantial rates of neurological impairment were identified in symptomatic individuals (41% Zaire, 40% Kenya, 66% Thailand, and 54% Brazil) (Maj et al. 1994). Similarly, Sacktor et al. (Sacktor et al. 2009) reported an approximate 30% prevalence of HAD in Uganda, and Wright and colleagues identified significant cognitive impairment in 11% of HIV-infected patients seen in ten different Asian Pacific sites. In contrast, neurocognitive impairment was rare in studies of HIV-infected individuals in Nairobi, Kenya, and in Zimbabwe (Parry et al. 1997; Mielke 2005; Jowi et al. 2007).

We assessed neurological and neuropsychological function in a large sample of ARV naïve HIV-infected persons in resource limited settings. We found a substantial prevalence of peripheral neuropathy (~20%), but somewhat unexpectedly, only 6% of participants were diagnosed with cognitive impairment. The severity of the diagnoses of peripheral neuropathy and HAD or MND was rated as subclinical or equivocal in most cases. Participants in this study were a subset of those enrolled in a larger study that examined treatment response to three different ARV regiments. We may have underestimated the prevalence and severity of neurological disease due to a selection bias. Specifically, a Karnofsky score of 70 or better was an inclusion criterion, thus selecting for individuals who were less likely to have neurological abnormalities. In addition, sites were encouraged to recruit subjects who they thought would be compliant and adhere to study procedures, potentially leading to a bias toward enrolling a healthier study population with less neurological impairment.

The neurological assessments and diagnoses varied considerably by country, with participants in Peru showing the lowest rates of neurological dysfunction (8%), diffuse CNS dysfunction (2%), focal CNS dysfunction (3%) and peripheral neuropathy (5%). The Zimbabwean cohort had the highest degree of overall neurological dysfunction (46%), diffuse CNS dysfunction (17%), focal CNS dysfunction (11%) and peripheral neuropathy (39%). This variation may simply have been due to differences in study populations. Although differences in administration of the neurological examination may have also played a role, care was taken to ensure that all study staff were appropriately trained to accurately perform the neurological examination.

The variation in neuropsychological test results between countries that we observed in this study was anticipated and has been seen in other studies. For example, in the World Health Organization (WHO) (Maj et al. 1994) study, results of the timed gait test were abnormal in 29% of symptomatic HIV-infected participants in Zaire, 22% in Kenya, 58% in Thailand, and 15% in Brazil. Such differences could be attributed to differences in study populations, languages, cultures, or demographic factors. One important factor in our study was differences in education across sites. For example, the median years of education ranged from 8 in Malawi to 12.5 in Peru. The results from Malawi were relatively lower, while Peru was relatively higher on a number of the tests, which may reflect educational level. As with the neurological examination, differences in test scores between sites could be due to variation in test administration. We minimized this possibility by on-site and central training sessions.

Different HIV subtypes likely predominated in the individual countries in which this study was conducted, and those differences may have contributed to the differences in neurological or neuropsychological performance that we observed. For example, Sacktor et al. (2009) documented that among a group of HIV-infected individuals in Uganda, those infected with subtype D had a greater prevalence of HIV associated neurological disease than those with subtype A. Clade was not formally assessed in this study, and remains to be determined. We found relatively poorer performance in Malawi, Zimbabwe, and India which are thought to be predominantly clade C countries, although this pattern did not hold in all countries thought to be predominantly clade C (South Africa). Relatively better performance was found in Peru and Thailand, thought to be predominantly clade B andr A/E respectively. This remains speculative at best until clade/subtype can be determined.

In the developed world, several studies show that initiation of HAART is associated with improvement in cognitive and peripheral nervous system function (Gendleman et al. 1998; Sacktor et al. 2002; McArthur et al. 2003; Robertson et al. 2004). We do not know whether these neurological benefits will be seen in HIV-infected patients in resource-limited settings who are treated with antiretrovirals. For example, while there is also evidence of a reduction in peripheral nervous system disease in the HAART era in the developed world, use of certain antiretroviral medications, particularly, stavudine, which is a common component of first line ARV regimens in resource-limited settings, may result in a neuropathy which is clinically indistinguishable from DSPN (Sacktor 2002; Schifitto et al. 2005).

HIV-associated cognitive impairment is associated with substantial impact on even the simplest activities of daily living and even minor decline may be relevant, as the burden of neurological disease on families and communities is substantial, with both an impact in terms of loss of productivity and income for the diagnosed, but also for those who take the primary responsibility as caretakers. In resource-limited settings with high rates of HIV-infection, the toll is likely devastating, but remains to be documented (Schifitto et al. 2001; Tozzi et al. 2004). The baseline results from this study document the current neurological and neuropsychological status in this unique treatment naïve group. Future longitudinal studies are required to address potential neurological benefits and harms of HAART in HIV-infected patients in resource-limited settings.

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References

1. Affandi JS, Price P, Imran D, Yunihastuti E, Djauzi S, Cherry CL. Can we predict neuropathy risk before stavudine prescription in a resource-limited setting? AIDS Res Hum Retroviruses. 2008; 24(10):1281–4. [PubMed: 18834321]
2. American Academy of Neurology. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection Report of a Working Group of the American Academy of Neurology AIDS Task Force. Neurology. 1991; 41(6):778–85. [PubMed: 2046917]
3. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69(18):1789–99. [PubMed: 17914061]
4. Belec L, Martin PMV, Vohito MD, Gresenguet G, Tabo A, Georges AJ. Low prevalence of neuropsychiatric clinical manifestations in central African patients with acquired immune deficiency syndrome. Trans R SOC Trop Med Hyg. 1989; 83:844–46. [PubMed: 2617657]
5. Elder GA, Sever JL. AIDS and neurological disorders: an overview. Anns Neurol. 1988; 23:S4–S6.
6. Gendleman H, Zheng J, Coulter C, Ghorpade A, Che M, Thylin M, Rubocki R, Persidsky Y, Hahn F, Reinhard J, Swindells S. Suppression of inflammatory neurotoxins by highly active antiretroviral therapy in HIV associated dementia. J Infect Diseases. 1998; 178:1000–7. [PubMed: 9806027]
7. Grey P, Berger P. Pain in women with HIV/AIDS. Pain. 2007; 132(1):S13–21. [PubMed: 17959310]
8. Howlett WP, Nkya WM, Mmni KA, Missalek WR. Neurological disorders in AIDS and HIV disease in the northern zone of Tanzania. J AIDS. 1989; 3:289–296.
9. Jowi JO, Mativo PM, Musoke SS. Clinical and laboratory characteristics of hospitalised patients with neurological manifestations of HIV/AIDS at the Nairobi hospital. East Afr Med J. 2007; 84(2): 67–76. [PubMed: 17598667]
10. Kumarasamy N, Venkatesh KK, Cecelia AJ, Devaleenal B, Lai AR, Saghayam S, Balakrishnan P, Yepthomi T, Poongulali S, Flanigan TP, Solomon S, Mayer KH. Spectrum of adverse events after generic HAART in southern Indian HIV-infected patients. AIDS Patient Care STDS. 2008; 22(4): 337–44. [PubMed: 18422462]

11. Maj M, Satz P, Janssen R, Zaudig M, Starace F, D'Elia L, Sughondhabirom B, Mussa M, Naber D, Ndetei D, Schulte G, Sartorius N. WHO Neuropsychiatric AIDS study, cross-sectional phase II. neuropsychological and neurological findings. Arch Gen Psyc. 1994; 51(1):51–61.
12. McArthur JC, Haughey N, Gartner S, Conant K, Pardo C, Nath A, Sacktor N. HIV associated dementia: A evolving disease. J of Neurovirol. 2003; 9:205–21. [PubMed: 12707851]
13. McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, Graham NM, McArthur JH, Selnes OA, Jacobson LP, Visscher BR, Concha M, Saah A. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology. 1993; 43(11):2245–52. [PubMed: 8232937]
14. Mielke J. Neurological complications of human immunodeficiency virus infection in Zimbabwe-2005. J Neurovirol. 2005; 11(3):23–5. [PubMed: 16540450]
15. Navia BA, Cho ES, Petito CK, Price RW. The AIDS dementia complex: Neuropathology. Ann Neurol. 1986; 19:525–35. [PubMed: 3014994]
16. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. clinical features. Ann Neurol. 1986; 19:517–24. [PubMed: 3729308]
17. Parry O, Mielke J, Latif AS, Ray S, Levy LF, Siziya S. Peripheral neuropathy in individuals with HIV infection in Zimbabwe. Acta Neurol Scand. 1997; 96(4):218–22. [PubMed: 9325472]
18. Price RW, Sidtis JJ. Evaluation of the AIDS Dementia Complex in clinical trials. J AIDS. 1990; 3(2):S51–60.
19. Price RW, Spudich SJ. Antiretroviral therapy and central nervous system HIV type 1 infection. J Infect Dis. 2008; 197(3):S294–306. [PubMed: 18447615]
20. Robertson KR, Hall CD. HIV related mild cognitive impairment and AIDS dementia complex. Semin in Neurol. 1992; 12(1):18–27.
21. Robertson KR, Robertson W, Ford S, Watson D, Fiscus S, Harp A, Hall C. Highly active antiretroviral therapy improves neurocognitive function. J AIDS. 2004; 36(1):562–66.
22. Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. J Neurovirol. 2002; 8(2):115–21. [PubMed: 12491162]
23. Sacktor N, McDermott MP, Marder K, Schifitto G, Selnes O, McArthur JC, Stern Y, Albert S, Palumbo D, Kieburtz K, Marcaida J, Cohen B, Epstein L. HIV-1 associated cognitive impairment before and after the advent of combination therapy. J Neurovirol. 2002; 8(2):136–42. [PubMed: 11935465]
24. Sacktor N, Nakasujja N, Skolasky RL, Rezapour M, Robertson K, Musisi S, Katabira E, Ronald A, Clifford DB, Laeyendecker O, Quinn TC. HIV subtype D is associated with dementia, compared with subtype A, in immunosuppressed individuals at risk of cognitive impairment in Kampala, Uganda. Clin Infect Dis. 2009; 49(5):780–6. [PubMed: 19622045]
25. Schifitto G, Kieburtz K, McDermott M, McArthur J, Marder K, Sacktor N, Palumbo D, Selnes O, Stern Y, Epstein L, Albert S. Clinical Trials in HIV associated cognitive impairment: Cognitive and functional domains. Neurology. 2001; 56:415–18. [PubMed: 11171916]
26. Schifitto G, McDermott MP, McArthur JC, Marder K, Sacktor N, McClernon DR, Conant K, Cohen B, Epstein LG, Kieburtz K. Markers of immune activation and viral load in HIV-associated sensory neuropathy. Neurology. 2005; 64(5):842–8. [PubMed: 15753420]
27. Sidtis JJ, Gatsonis C, Price RW, Singer EJ, Collier AC, Richman DD, Hirsch MS, Schaerf FW, Fischl MA, Kieburtz K, Simpson D, Koch M, Feinberg J, Dafni U. Zidovudine treatment of the AIDS dementia complex: results of a placebo controlled trial. AIDS Clinical Trials Group. Ann Neurol. 1993; 33:343–9. [PubMed: 8489204]
28. Simpson DM, Kitch D, Evans SR, McArthur JC, Asmuth DM, Cohen B, Goodkin K, Gerschenson M, So Y, Marra CM, Diaz-Arrastia R, Shriver S, Millar L, Clifford DB. HIV neuropathy natural history cohort study. Neurology. 2006; 66:1679–87. [PubMed: 16769940]
29. Tozzi V, Balestra P, Galgani S, Murri R, Bellagamba R, Narciso P, Antinori A, Giulianeli M, Tosi G, Costa M, Sampaolesi A, Fantoni M, Noto P, Ippolito G, Wu A. Neurocognitive performance and quality of life in patients with HIV infection. AIDS Human Retrovir. 2004; 19(8):643–52.
30. World Health Organization. World Health Organization. 1993. Global summary of the HIV/AIDS epidemic, December 2003. Geneva, Switzerland. December, 2003

31. Wright E, Brew B, Arayawichanont A, Robertson K, Samintharapanya K, Kongsaengdao S, Lim M, Vonthanak S, Lal L, Sarim C, Huffam S, Li P, Imran D, Lewis J, Lun WH, Kamarulzaman A, Tau G, Ali ST, Kishore K, Bain MP, Dwyer R, McCormack G, Hellard M, Cherry C, McArthur J, Wesselingh S. Neurologic disorders are prevalent in HIV- positive outpatients in the Asia-Pacific region. Neurology. 2008; 71(1):50–6. [PubMed: 18591505]

Table 1

Screening CD4+ Cell Counts and Plasma HIV RNA by Country

		Country							
		Total	**Brazil**	**India**	**Malawi**	**Peru**	**South Africa**	**Thailand**	**Zimbabwe**
CD4 count (cells/mm^3)	Median	172.5	183	198	178	167	157	125	170.5
	Q1, Q3	97.5, 232.0	75, 257	136,236	122, 232	88, 234	100, 216	37, 177	98.5,217.5
Log_{10} Plasma HIV-1 RNA (copies/ml)	Median	5.0	5.2	5.1	4.8	4.8	5.2	5.0	5.2
	Q1, Q3	4.5, 5.5	4.7, 5.6	4.5, 5.5	4.4, 5.2	4.2, 5.1	4.6, 5.7	4.6, 5.3	4.6, 5.6
Sex	Male	408	102	102	39	37	60	37	31
	Female	452	59	82	94	25	107	36	49
Age	Median	34	36	33	31	33	34	33	36
	<20 years	5	1	0	1	0	2	1	0
	20-29	251	45	53	44	25	47	23	14
	30-39	376	51	105	63	24	63	30	40
	40-49	179	46	22	19	11	45	17	19
	50-59	42	13	3	5	2	10	2	7
	60+	7	5	1	1	0	0	0	0
Education Level	Median	10	9	9	8	12.5	11	10	11
	Q1, Q3	7, 12	6, 11	6, 11	4, 11	11, 14	9, 12	6, 15	8.5, 12.5

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Table 2

Neurologic Assessment for Evaluable Patients at Week 0, Stratified by Country

		Country							
		Total (N=860)	**Brazil (N=161)**	**India (N=184)**	**Malawi (N=133)**	**Peru (N=62)**	**South Africa (N=167)**	**Thailand (N=73)**	**Zimbabwe (N=80)**
Overall neurologic assess normal? (p-value *<0.001)	Yes	610 (71%)	99 (61%)	151 (82%)	103 (77%)	57 (92%)	138 (83%)	19 (26%)	43 (54%)
	No	249 (29%)	61 (38%)	33 (18%)	30 (23%)	5 (8%)	29 (17%)	54 (74%)	37 (46%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neuro dysfunction (all neuro diagnoses) (p-value *<0.001)	Normal	707 (82%)	154 (96%)	153 (83%)	132 (99%)	57 (92%)	148 (89%)	19 (26%)	44 (55%)
	Equivocal/Subclinical	142 (17%)	5 (3%)	29 (16%)	1 (1%)	5 (8%)	16 (10%)	54 (74%)	32 (40%)
	Mild	9 (1%)	1 (1%)	2 (1%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	4 (5%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Neuro dysfunction (peripheral neuropathy) (p-value *<0.001)	Normal	656 (76%)	109 (68%)	157 (85%)	111 (83%)	59 (95%)	149 (89%)	22 (30%)	49 (61%)
	Equivocal/Subclinical	175 (20%)	50 (31%)	2 (1%)	22 (17%)	3 (5%)	16 10%)	51 (70%)	31 (39%)
	Mild	1 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Moderate	2 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	25 (3%)	0 (0%)	24 (13%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Neuro dysfunction (focal CNS disease) (p-value *=0.014)	Normal	807 (94%)	155 (96%)	159 (86%)	128 (96%)	60 (97%)	161(96%)	72 (99%)	72 (90%)
	Equivocal/Subclinical	22 (3%)	5 (3%)	0 (0%)	5 (4%)	2 (3%)	3 (2%)	1 (1%)	6 (8%)
	Mild	5 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	2 (3%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	25 (3%)	0 (0%)	24 (13%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Neuro dysfunction (diffuse CNS disease) (p-value *<0.001)	Normal	779 (91%)	141 (88%)	154 (84%)	123 (92%)	61 (98%)	160 (96%)	73 (100%)	67 (84%)
	Equivocal/Subclinical	51 (6%)	18 (11%)	5 (3%)	10 (8%)	1 (2%)	6 (4%)	0 (0%)	11 (14%)
	Mild	4 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

* Monte Carlo estimate of the exact p-value

Table 3

MND and HAD for Evaluable Patients at Week 0, Stratified by Country

			Country						
		Total (N=860)	**Brazil (N=161)**	**India (N=184)**	**Malawi (N=133)**	**Peru (N=62)**	**South Africa (N=167)**	**Thailand (N=73)**	**Zimbabwe (N=80)**
MND (p-value *<0.001)	Yes	51 (6%)	18 (11%)	5 (3%)	10 (8%)	1 (2%)	6 (4%)	0 (0%)	11 (14%)
	No	783 (91%)	142 (88%)	155 (84%)	123 (92%)	61 (98%)	160 (96%)	73 (100%)	69 (86%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	25 (3%)	0 (0%)	24 (13%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
HAD (p-value *=0.014)	Yes	4 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
	No	830 (97%)	159 (99%)	159 (86%)	133(100%)	62 (100%)	166 (99%)	73 (100%)	78 (98%)
	Did not assess	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	25 (3%)	0 (0%)	24 (13%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)

*Monte Carlo estimate of the exact p-value

Table 4

Baseline Diagnoses

Diagnoses (n=859*)	#	%	Exact 95% CI (%,%)
Toxoplasmic Encephalitis	0	0	(0, 0.40)
Neurosyphilis	0	0	(0, 0.40)
Coccidioidal Meningitis	0	0	(0, 0.40)
Cryptococcal Meningitis	2	0.23	(0.01, 0.86)
Mycobacterial Infect (non-TB, non-MAC)	0	0	(0, 0.40)
Extra Pulmonary Tuberculosis	13	1.51	(0.83, 2.60)
Tuberculosis	37	4.31	(3.02, 5.87)
CNS Tuberculosis	2	0.23	(0.01, 0.86)
CMV Encephalitis	0	0	(0, 0.40)
Pro. Multi. Leukoencephalopathy (PML)	0	0	(0, 0.40)
Varicella Zoster	8	0.93	(0.38, 1.84)
Primary CNS Lymphoma	0	0	(0, 0.40)
CNS Mass Lesion - etiology unknown	0	0	(0, 0.40)
Stroke	2	0.23	(0.01, 0.86)
Diagnoses (n=859*)	#	%	Exact 95% CI (%,%)
Transient Ischemic Attack	0	0	(0, 0.40)
Alcohol Abuse	0	0	(0, 0.40)
Other Substance Abuse	2	0.23	(0.01, 0.86)
Depression	11	1.28	(0.62, 2.28)
Epilepsy	0	0	(0, 0.40)
Seizure Disorder (not epilepsy)	0	0	(0, 0.40)
Focal Neurological Deficit	2	0.23	(0.01, 0.86)
Gait or Balance Disorder	0	0	(0, 0.40)
Mental Status Impairment	4	0.47	(0.12, 1.18)
Mood Disorders	2	0.23	(0.01, 0.86)
Chagas with CNS Involvement	0	0	(0, 0.40)
HIV-associated Neuromuscular Weakness	0	0	(0, 0.40)
Hypomania	0	0	(0, 0.40)

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Diagnoses (n=859*)	**#**	**%**	**Exact 95% CI (%,%)**
Psychosis	0	0	(0, 0.40)
Suicidal Ideation	5	0.58	(0.17, 1.38)
Hallucinations	1	0.12	(0.01, 0.68)
Insomnia	4	0.47	(0.12, 1.18
Diagnoses (n=859 *)	#	%	Exact 95% CI (%,%)
Drowsiness	3	0.35	(0.07, 1.04)
Dream Abnormality	2	0.23	(0.01, 0.86)
Other Psychiatric Disease (specified below)	1	0.12	(0.01, 0.68)
SCHIZOPHRENIA	1		
Other Neurologic System Disease (specified below)	3	0.35	(0.07, 1.04)
HEAD INJURY - HEARING PROBLEM	1		
OLD BELL'S PALSY	1		
PH NEURALGIA, VISUAL LOSS	1		
Other CNS Disease (specified below)	2	0.23	(0.01, 0.86)
ISOLATED MEMORY DEFICIT	1		
MINOR COGNITIVE DEFICIT	1		
Other Peripheral Nerve Disease (specified below)	9	1.05	(0.46, 1.96)
INH NEUROPATHY	2		
ISONIAZID INDUCED NEUROPATHY	1		
ISONIAZID NEUROPATHY	1		
LEFT LUMBAR RADICULOPATHY	1		
POSSIBLE BRACHIAL PLEXUS INJUR	1		
RIGHT PERIPHERIC FACIAL PALSY	1		
SENSORY-MOTOR NEVROPATHY	1		
TUNNEL CARPAL SYNDROME	1		
Diagnoses (n=859 *)	#	%	Exact 95% CI (%,%)
Other Disease/Disorder (specified below)	9	1.05	(0.46, 1.96)
ARTHRITIS OF BOTH KNEES & FEET	1		
BACTERIAL MENINGITIS	1		
BILATERAL GLAUCOMA	1		

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Diagnoses (n=859*)	#	%	Exact 95% CI (%, %)
HIPOGENESIA INTERPHALANGE LEFT	1		
OROPHARYNGEAL CANDIDIASIS	1		
PENICILLIOSIS	1		
POOR EYE SIGHT	1		
PSORIASIS	1		
TINGLING BOTH FEET	1		

* Missing 1 subject

Table 5

Baseline Neuropsychological Test Results

		Country						
		Total	**Brazil**	**Malawi**	**Peru**	**South Africa**	**Thailand**	**Zimbabwe**
Grooved Peg Dom (s)	Mean	81.9	77.5	94.7	71.4	80.1	65.9	94.3
	Standard deviation	28.1	21.0	30.3	17.1	29.0	19.0	43.8
Grooved Peg Non-Dom (s)	Mean	90.5	81.8	105.6	79.8	88.4	70.9	106.9
	Standard deviation	29.6	23.2	32.7	24.1	20.9	15.9	48.0
Semantic Verbal Fluency (# words)	Mean	16.2	16.0	13.1	20.8	18.3	18.8	14.0
	Standard deviation	5.8	5.2	3.9	4.9	7.5	5.7	3.4
Timed Gait (s)	Mean	12.9	14.0	14.3	11.8	11.6	11.7	12.5
	Standard deviation	2.4	2.5	2.7	1.7	2.4	1.3	1.8
Finger Tap Dom (# taps)	Mean	38.3	38.7	31.0	32.4	37.8	45.9	50.0
	Standard deviation	11.9	13.3	10.2	8.8	10.5	9.6	10.5
Finger Tap Non-Dom (# taps)	Mean	35.7	37.0	29.2	31.0	34.7	41.8	46.0
	Standard deviation	10.2	10.3	9.8	6.9	9.8	7.2	9.6