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ABSTRACT

Background and Objective.

A5199 is an ongoing study to evaluate the prevalence and incidence of neurological disease in 860 persons with HIV-1 and the impact of antiretroviral (ARV) therapy on neurological disease in resource limited settings (RLS).

Methods.

Participants were enrolled in Brazil, India, Malawi, Peru, South Africa, Thailand and Zimbabwe. Standardized neurological and neuropsychological (NP) exams (grooved pegboard, timed gait, semantic verbal fluency, and finger tapping) were administered every 24 weeks. The present analysis was limited to 293 participants who were randomized to treatment with didanosine enteric-coated (ddl) + emtricitabine (FTC) + atazanavir (ATV) in Arm 1B of ACTG Study A5175 (PEARLS). Changes in neurological and neuropsychological function were analyzed with linear and logistic GEE regression models.

Results.

Baseline characteristics were 54% female, 48% Black, median (Q1, Q3) screening CD4 of 182 (96, 235), median (Q1, Q3) entry plasma HIV-1 RNA log₁₀ 5.0 c/mL (2.6, 5.9). Abnormal baseline assessments included: 29% with abnormal overall neurological assessment, 23% with neuropathy, 6% with focal CNS disease, 10% with diffuse CNS disease, 6% with mild neurocognitive disorder (MND), and 1% with HIV Associated Dementia (HAD). Significant improvements in neuropsychological functioning ($p < 0.01$ for all tests) after ARV initiation were observed after controlling for baseline function, age, sex, country, CD4, plasma HIV-1 RNA stratum, and years of education although effect sizes were modest and varied by country. The odds of neuropathy ($p = 0.03$, OR=0.81, 95% CI 0.67, 0.98) and focal CNS disease ($p = 0.02$, OR=0.46, 95% CI 0.24, 0.88) decreased for each additional 24 weeks of follow-up after controlling for the above covariates. Significant changes in overall neurological function or diffuse CNS disease were not observed. HAD, MND, and other neurological diagnoses were uncommon.

Conclusions.

Significant improvement in neuropsychological function occurred after initiation of ARV in RLS. The magnitude of improvement in NP performance varied by country. Improvements may be due to control of HIV through ARV effects or practice effects, or both. Variation in neuropsychological performance across countries could reflect differences in population characteristics, test administration, HIV-1 subtypes, or ARV resistance patterns. Future work will address these issues.

INTRODUCTION

Little is known about neurological disease in international resource limited settings where the vast majority of HIV infection occurs.

We report the data from the 1B arm of ACTG A5199: The International Neurological Study.

The present analysis was limited to 293 participants who were randomized to treatment with didanosine enteric-coated (ddl) + emtricitabine (FTC) + atazanavir (ATV) in ACTG Study A5175 (PEARLS). A Data/Safety Monitoring Board planned interim review of PEARLS on 6-May-2008 found that ddl+FTC+ATV had inferior outcome compared to ZDV/3TC+EFV. In response to the DSMB finding Arm 1B was closed and study participants were switched to alternate study-provided ARVs.

This is the first follow up data available from ACTG 5199.

METHODS

Design

Participants

- Antiretroviral naïve
- CD4+ cells < 300
- Overall 860 subjects enrolled
- Arm 1B 293 subjects

International Sites

- 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
- Harare, Zimbabwe

Treatment Regimens

Arm 1B - FTC/ATV/DDI

Neuropsychological evaluation

- Timed Gait
- Grooved Pegboard
- Finger Tapping
- Semantic Verbal Fluency

Neurological evaluation

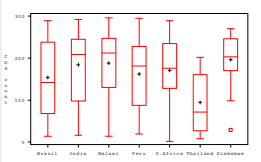
- History, Symptoms, Exam:
 - Cognitive, Motor, Sensory, Reflex
- Neurologic Formulation:
 - Summary of Severity, Duration, Course
- AIDS Dementia

Participants

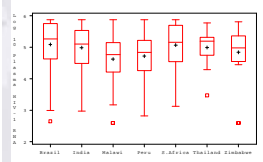
58 Brazil
 62 India
 46 Malawi
 24 Peru
 54 South Africa
 22 Thailand
 27 Zimbabwe



Screening CD4 by Country

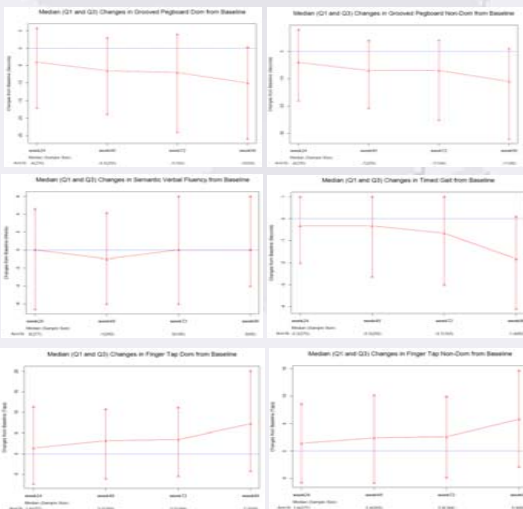


Entry HIV RNA by Country



+ mean. Bar median. Box 1st – 3rd quartiles.
 Whiskers largest/smallest observation within range of 1.5 IQR above Q3/below Q1.

Neuropsychological Performance



Significant improvements ($p < .05$) in NP functioning (except Verbal Fluency) after ARV initiation were observed after controlling for baseline function, age, sex, country, CD4, plasma HIV-1 RNA stratum, and years of education although effect sizes were modest and varied by country. All directions of change reflect improvement (decreases in latency for grooved pegboard, timed gait; increases in finger taps).

Blue line - Baseline score. Red line - Median change from baseline. Whisker - 1st Quartile (25%) and 3rd Quartile (75%).

RESULTS

Demographics

- Gender
 - Male 134 (46%)
 - Female 159 (54%)
- IV Drug use 1/293 (0%)
- Age
 - Median 34 yrs
- Education
 - Median 10 yrs, Q1=7, Q3=12

Participants on Arm 1B

293 Baseline
 284 Week 24
 265 Week 48
 189 Week 72
 62 Week 96
 5 Week 120

Longitudinal Follow up

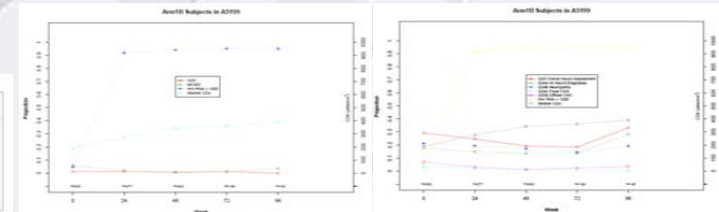
- Significant improvements in NP function were found over time

- There was variation in NP improvements by country

- No significant variation in improvement was found across viral load strata, except in fingertapping dominant hand

- No significant variation in improvement was found across CD4 strata

- Decreases in the proportions of participants with neurological abnormalities, HAD, and MND at week 24, 48 and 72



CONCLUSIONS

There were significant improvements in neuropsychological function after initiation of antiretroviral therapy in resource limited settings.

We found that the magnitude of this improvement in neurocognitive performance varied by country.

Improved neurocognitive functioning may be due to control of HIV viral load through ARV effects, or practice effects, or both.

Variation in NP performance across countries could reflect differences in population characteristics, test administration, HIV-1 subtypes, ARV resistance patterns or some combination of these effects.

Ongoing follow up of subjects is underway.

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