

# Neurocognitive function at first-line failure and on second-line antiretroviral therapy in Africa:

## Analyses from the EARNEST Trial

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## **ABSTRACT**

### Objective

To assess neurocognitive function at first-line antiretroviral therapy failure and change on second-line therapy

### Design

Randomized controlled trial conducted in 5 sub-Saharan African countries.

### Methods

Patients failing first-line therapy according to WHO criteria after >12 months on NNRTI-based regimens were randomised to second-line therapy (open-label) with lopinavir/ritonavir (400mg/100mg twice daily) plus either 2-3 clinician-selected NRTIs, raltegravir, or as monotherapy after 12 weeks induction with raltegravir. Neurocognitive function was tested at baseline, weeks 48 and 96 using colour trails tests 1 and 2, and the grooved pegboard test. Test results were converted to an average of the 3 individual test z-scores.

### Results

1036 patients (90% of those >18y enrolled at 13 evaluable sites) had valid baseline tests (58% female, median 38 years, viral load 65,000 c/ml, CD4 count 73 cells/mm<sup>3</sup>). Mean (SD) baseline z-score was -2.96 (1.74); lower baseline z-scores were independently associated with older age, lower body weight, higher viral load, lower haemoglobin, less education, fewer weekly working hours, previous CNS disease, and taking fluconazole ( $P<0.05$  in multivariable model). Z-score increased by mean (SE) of +1.23 (0.04) after 96 weeks on second-line therapy ( $P<0.001$ ;  $n=915$  evaluable), with no evidence of difference between the treatment arms ( $P=0.35$ ).

## Conclusions

Patients in sub-Saharan Africa failing first-line therapy had low neurocognitive function test scores, but performance improved on second-line therapy. Regimens with more CNS-penetrating drugs did not enhance neurocognitive recovery indicating this need not be a primary consideration in choosing a second-line regimen.

## Introduction

Highly-active antiretroviral therapy (HAART) improves survival and quality-of-life among HIV-infected individuals.<sup>1</sup> The remarkable increase in access to HAART in resource-limited settings (RLS) over the past decade, as well as the current global efforts towards earlier HAART initiation, have amplified the benefits of HIV treatment including the impact on HIV-associated neurocognitive disorders (HAND). The introduction of HAART has been associated with strong reductions in prevalence of HIV-associated dementia (HAD)-the most severe form of HAND. However the impact of HAART on the milder forms of HAND including mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI) is less certain.<sup>2 3</sup> MND and ANI are still common findings in HIV cohorts in the HAART era.<sup>4 5</sup> It has been suggested that ART regimens including drugs with higher levels of CNS penetration might have greater benefit on HAND, although evidence for this is contradictory.<sup>6 7 8 9 10</sup> The magnitude, severity and factors associated with HAND (including MND and ANI), as well as the response of HAND to antiretroviral therapy, have been fairly well characterized in resource-rich settings, but data from resource-limited settings (RLS) are more limited.<sup>11 12 13</sup> RLS studies indicate that HAND is common, with significant regional differences in prevalence (ranging from 25%-61%),<sup>14 15 16</sup> and has similar risk factors as HAD, including low CD4 counts, older age, and male gender.<sup>17 18</sup> However, few studies have characterized the prevalence of neurocognitive impairment among individuals failing first-line HAART in either RLS or resource-rich settings, and data on neurocognitive responses on second-line therapy are even more limited.

Here, we report prospective neurocognitive function measurements using a simple standardised battery of tests in a large multicentre trial of second-line therapy in Africa.<sup>19</sup>

The aim of this study was to examine the magnitude of and factors associated with neurocognitive impairment at the time of first-line regimen failure and assess how neurocognitive function changed over 96 weeks on 3 different PI based second-line regimens.

## Methods

The current study was conducted within the large multi-centre Europe Africa Research Network for Evaluation of Second-line Therapy (EARNEST) trial. Briefly, EARNEST was an open-label, randomized parallel-group trial (ISRCTN-37737787) performed in 14 centres in 4 sub-Saharan African countries. It enrolled HIV-infected patients >12 years who were failing first-line HAART (according to WHO clinical, immunological and/or virological criteria). Participants were randomly assigned 1:1:1 to receive a ritonavir-boosted protease inhibitor (PI), standardised to lopinavir/ritonavir 400mg/100mg twice daily, with either (i) 2-3 new or recycled nucleoside-reverse-transcriptase-inhibitors (NRTIs) chosen without genotyping by the treating doctor (PI/NRTI); (ii) raltegravir 400mg twice daily (PI/RAL); or (iii) raltegravir induction for 12 weeks only (PI-mono). Additional details including the eligibility criteria, study design and site settings are described elsewhere.<sup>14</sup>

The study (including the neurocognitive assessments as part of the main trial protocol) was approved by ethics committees and regulatory agencies in participating countries and the UK. All participants provided written informed consent.

### ***Neurocognitive assessment***

Neurocognitive function was assessed in all participants at baseline (first-line treatment failure) and at week 48 and week 96 using three simple neurocognitive tests, chosen to reflect frontal sub-cortical functions, the most common neurocognitive impairments seen in HIV-infected individuals.<sup>20</sup> The Colour trails tests are two-part tests that assess the attention/concentration domain as well as the cognitive flexibility within the executive functioning domain<sup>21</sup>. The Grooved Pegboard test assesses psychomotor speed and fine motor function in both, dominant and non-dominant hands.

This simple battery of widely-used tests was selected to suit the clinical environments in resource-limited settings that are often extremely busy and have no specialized neurocognitive test operators.

The tests were administered by a clinician or research nurse. Quality assurance measures were the use of a standardized testing manual across all study sites, initial and annual training of site staff who were designated to perform the tests, restriction of test performance to the designated staff, and on-site monitoring of a random selection of tests to identify systematic errors in execution.

Each neurocognitive test score was standardised using demographic-adjusted normative means of US origin (predominantly Caucasian ethnicity) to give a z-score.<sup>22 23</sup> This was adjusted for age, and level of education for the colour trail scores, and age alone for the grooved pegboard scores.

The z-scores for each hand on the grooved pegboard were averaged, and then combined with the z-scores for the colour trail 1 and colour trail 2 tests to give an average z-score (NPZ-3 score) at each assessment.<sup>24</sup>

Normative means for the grooved pegboard data were not available for participants <18 years so they were excluded from analyses. On-site monitoring identified concerns over the procedures used during baseline testing at one site (one out of the 8 sites in Uganda) so this site was excluded from primary analyses, but included in a sensitivity analysis.

### ***Statistical Analysis***

We assessed the influence of the following risk factors on NPZ-3 scores at first-line failure: age, sex, weight, BMI, ART history, viral load, CD4, WHO stage, history of CNS disease, family history of cardiovascular disease, diabetes, alcohol exposure, smoke exposure, haemoglobin, creatinine, social economic factors (availability of food, years of education, employment status, household monthly income), and concomitant medication.

Years on first-line ART and creatinine were truncated at approximate 99<sup>th</sup> percentiles (to avoid undue influence of extreme outliers on the estimated associations). At baseline, the unadjusted association between NPZ-3 score and each factor was modelled using complete case univariable linear regression with continuous factors modelled using fractional polynomials (FP) to allow for non-linear relationships with NPZ-3 score. Factors with univariable  $p < 0.2$  were included in a multivariable linear regression which used backward selection (exit criteria  $p = 0.1$ ) to select independent risk factors using multiple FPs to allow for non-linear relationships. In the multivariable analysis multiple imputation using *Stata's* *mi* *impute* command (25 imputations) was used to account for missing risk factor data and missing test times where at least 2 of the 4 test times were known. Sensitivity analyses used only complete cases, or colour trail norms from an African-American population, or colour trail and grooved pegboard means from an HIV-negative Ugandan population.<sup>25</sup>

Mean change in NPZ-3 scores from baseline were compared between the 3 treatment arms at weeks 48 and 96 using t-tests and ANOVA; generalized estimating equations (GEE) (independent correlation structure with robust variance, normal distribution) were used to test differences between arms across all weeks.

GEE (independent correlation structure with robust variance, normal distribution) were also used to investigate the effect of the factors selected in the baseline model on NPZ-3 scores at weeks 48 and 96 (complete cases only), where possible time-updated factors were used.

Statistical tests presented are two-sided. All analyses were carried out in *Stata*® version 13.1.

## Results

A total of 1277 individuals were enrolled into the EARNEST trial and randomized across the 3 treatment arms. Analysis of the main trial primary outcome (good disease control at week 96) demonstrated that PI/RAL was not superior to boosted PI/NRTI ( $p=0.21$ ) but was non-inferior. PI-mono was not non-inferior to boosted PI/NRTI, and the arm was discontinued after week 96 due to markedly lower viral suppression and increased risk of the emergence of resistance mutations. Baseline characteristics and other outcomes across the 3 study arms were similar and are described elsewhere.<sup>14</sup>

Of the 1156 evaluable participants at first-line failure (excluding 74 aged <18 years and 47 from the single site with implementation inconsistencies), 1036 (90%) had valid results for all 3 neurocognitive test domains (supplementary table 1). The main reasons for invalid tests were illiteracy ( $n=102$  tests) and poor vision ( $n=51$  tests) (supplementary table 2). The mean $\pm$ sd z-score for colour trails 1 and 2 were  $-3.72\pm2.37$ , and  $-2.73\pm2.16$  respectively, and for the combined pegboard z-score was  $-2.63\pm2.20$  (supplementary table 3).

### ***Factors Associated with neurocognitive function at Baseline***

The mean $\pm$ sd NPZ-3 score at first-line failure was  $-2.96\pm1.74$ . Tables 1 and 2 show the unadjusted univariable and adjusted multivariable associations with NPZ-3 score at first-line failure respectively.

In the adjusted multivariable model (Table 2), NPZ-3 scores at first-line failure were significantly lower in patients who were older (change in Z-score per 10 years older  $-0.25$  (95% CI  $-0.35,-0.14$ )  $p<0.0001$ ), had lower body weight (per 10 kg heavier  $+0.12$  (0.02,0.21)  $p=0.01$ ), higher viral loads (per doubling  $-0.07$  ( $-0.12,-0.03$ )  $p=0.002$ ), lower hemoglobin (per 1mg/dl higher  $+0.16$  ( $+0.11,+0.21$ )  $p<0.0001$ ), fewer years of education (per doubling  $+0.39$  ( $+0.26,+0.52$ )  $p<0.0001$ ), worked fewer hours per week (per 10 hours

longer +0.09 (+0.05,+0.14)  $p<0.0001$ ), had a previous CNS disease (-0.45 (-0.82,-0.08)  $p=0.02$ ), or had taken fluconazole in the last 10 weeks (-0.61 (-0.99,-0.22)  $p=0.002$ ).

There was a trend towards NPZ-3 scores also being lower in those with lower CD4 cell count (per 100 cells/mm<sup>3</sup> higher +0.10 (-0.00, +0.21)  $p=0.06$ ), lower household monthly income (vs <\$50: \$50-\$200 +0.29 (+0.03, +0.54); >\$200 +0.21(-0.15, +0.56);  $p=0.08$ ), and not taking dapsone in the last 10 weeks (+0.55 (-0.09, +1.19)  $p=0.09$ ).

Significant unadjusted effects of prior ART exposure, availability of regular meals, employment status, and other concomitant medication were no longer independent predictors after adjusting for the characteristics above.

All sensitivity analyses gave broadly comparable results (supplementary tables 4-8).

### ***Neurocognitive Response to Treatment***

Overall, the NPZ-3 score increased on second-line therapy with a mean $\pm$ SE change across all three study arms of +0.91 $\pm$ 0.04 and +1.23 $\pm$ 0.04 at week 48 and week 96 respectively ( $P<0.001$ ). There was no statistically significant difference between the second-line regimens (Table 3 and Figures 1a and 1b) ( $p>0.2$ ).

At week 48 and 96, NPZ-3 scores were no longer associated with viral load (current viral load  $p=0.69$ , viral load at failure  $p=0.38$ ), years of education at failure ( $p=0.19$ ), current hours worked per week ( $p=0.20$ ), CNS disease prior to current time ( $p=0.70$ ), fluconazole use prior to current time ( $p=0.70$ ), or taking dapsone in the 10 weeks before failure ( $p=0.55$ ) but remained associated ( $p<0.05$ ) with all other factors that were significantly related to baseline function as listed above (supplementary table 9).

## Discussion

In this analysis of a large second-line ART trial in Africa, we report reduced neurocognitive function scores among individuals failing first-line therapy. The scores were significantly lower in patients who were older, had lower body weight, higher viral load, lower haemoglobin, fewer years of education, fewer working hours, previous CNS disease, and who were taking fluconazole. Neurocognitive function improved after starting second-line ART with no significant difference observed between the 3 study arms.

The very low z-scores we observed in our patients may in part be a function of the norms used for adjustment that were derived from a healthy, mostly Caucasian, American population. The same American normative datasets have been shown to produce inadequate adjustment of neurocognitive function in African HIV-positive patients living in the UK and the limitations may be even greater for our trial population.<sup>26</sup> In a sensitivity analysis, we normalized results using a small dataset of HIV negative individuals from Uganda (Supplementary Table 7), and found that evidence of neurocognitive impairment persisted but the magnitude of this effect was reduced markedly.<sup>27</sup> Although different normative datasets will generate different relative levels of impairment, the comparison with Ugandan norms together with the independent associations between scores at first-line failure and multiple HIV disease-related factors regardless of normative data used suggest that much of this impairment is likely to be genuine.

Similar to most other studies, we observed that lower NPZ-3 scores were associated with higher viral loads at first-line failure after adjusting for other factors.<sup>28,29</sup> HIV is a neurotropic virus that has both direct and indirect pathogenic effects on the CNS, and patients failing first-line ART in Africa often have very high viral loads (in the peripheral circulation but also possibly in the CNS) due to late detection of treatment failure because monitoring is largely clinical and immunological with no routine HIV viral load

monitoring. We also found a weak association at first-line failure between CD4 count and NPZ-3 score independent of viral load. It is noteworthy that patients with a previous CNS disease had lower NPZ-3 scores at first-line failure. CNS diseases are a very common manifestation of HIV disease in Africa. Infections like cryptococcal meningitis not only cause considerable mortality in these settings, but can also leave critical damage to the CNS. We observed that taking fluconazole was an independent predictor of lower neurocognitive function even after adjusting for previous CNS disease. It could be that patients taking fluconazole were generally sicker in a variety of ways than those who were not taking this medication. These multiple disease-related associations indicate that the cause of severe neurocognitive impairment is likely multifactorial, in keeping with the heterogeneity of patients' clinical condition at the time of first-line failure.

The study also found a strong independent association between age as well as years of education and NPZ-3 scores among patients failing first-line ART. These factors are well known to influence neurocognitive function which is why neurocognitive data are usually presented as z-scores that attempt to adjust for these factors. The residual associations we have observed are likely to represent incomplete adjustment. Although the colour trail tests were adjusted for age and education level, the pegboard scores were adjusted for age only.

Our study additionally provides the first substantive data on the changes in neurocognitive function on second-line therapy in a large population. We found evidence of improvement in neurocognitive function 48 weeks after starting second-line therapy which continued to week 96. This indicates that at least some of the excess impairment associated with first-line failure is likely to be reversible and is a further illustration of the clinical benefits (aside from avoidance of death and opportunistic infections) that may accrue from starting patients with ART failure on second-line therapy.

The similarity of the improvement of neurocognitive function across the three study arms is surprising for several reasons. Firstly, the PI-mono arm had markedly worse systemic virologic suppression rates, which has been associated with progression of CNS disease.<sup>30</sup> Secondly, the two combination arms had greater CNS penetration effectiveness (CPE) score than the PI-mono arm (PI/NRTI combined score of 6, based on TDF/3TC as the commonest NRTI selection; PI/RAL combined score of 6 ; PI-mono score of 3) often considered to be related to neurocognitive outcomes.<sup>31</sup> Although superior neurocognitive recovery might have been expected in the NRTI-containing arm given that CNS penetration of this class is well established, most of the patients in this arm were taking lamivudine with tenofovir which has the lowest CPE in this class. Raltegravir and lopinavir have similarly good CPE scores and we would therefore have expected an improved NC response in the arm in which they were combined.

The similar response in the 3 arms suggests that the general response to ART (including recovery in general health, recovery from opportunistic infections, and improvement in mental status and nutritional status) rather than CNS drug penetration is the key determinant of neurocognitive function among patients on ART. The longitudinal changes in neurocognitive function and comparisons across study arms are likely to be reliable, less dependent on the validity of normative data described above.

Additional possible limitations of this study are that we used a smaller test battery (3 domains) and it is possible that a more comprehensive battery might have given a different picture. Because key function domains such as learning and memory were not explored, we cannot tell whether the observed recovery with second-line is limited to the motor domains with possible persistence or even progression of poor performance on other cognitive function domains. However, pragmatic considerations made use of a more comprehensive neurocognitive test battery impossible given the scale of the study with over 1000 patients tested on repeat occasions, located across a diversity of sites and challenging settings.

We have shown that this short battery of well-established tests can detect changes in response to therapy.

Moreover, this test battery was performed by non-specialists and has the potential to be rolled out in real world settings to document prospective NCI changes on ART. As with all such studies, we cannot exclude the possibility that practice effects contributed to some of the observed improvements in neurocognitive function over time. However, an HIV clinical trial in clinically stable patients that applied a similar brief battery of tests at annual intervals found an increase in NPZ-5 score of 0.53 after 3-5 years follow-up,<sup>32</sup> and a similarly modest change (NPZ-5 increase of 0.13) was observed in a trial that re-tested stable patients with a similar battery after 6 months.<sup>33</sup> Thus it is unlikely that practice effects alone would explain the magnitude of change in neurocognitive function (increase in NPZ-3 score of 1.2 over 96 weeks) that we observed. Lastly, we did not systematically evaluate participants for depression and therefore did not determine its influence on neurocognitive function test results.<sup>34</sup>

In summary, our study suggests that neurocognitive function is reduced among individuals failing first-line HAART. We documented improvements in neurocognitive function that occur on second-line ART irrespective of the antiretroviral regimens used in the study, suggesting that the penetration of drugs into the CNS may not be a primary consideration in selecting a second-line regimen. These findings may provide an additional justification for timely identification of first-line failure and switch to second-line therapy.

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