

**Supplementary Table 1: Pattern of missing tests at first-line failure**

Pattern (1=test done, 0 =test missing)				Frequency
Pegboard-d	Pegboard-nd	CT 1	CT2	N=1156 <sup>a</sup>
1	1	1	1	1036
1	1	0	0	66
1	1	1	0	23
0	0	0	0	17
1	1	0	1	4
1	0	1	1	3
0	0	1	1	3
1	0	0	0	2
1	0	1	0	1
0	1	1	1	1

<sup>a</sup> Excluding all tests from one site with implementation inconsistencies and patients who were under 18 at enrolment Pegboard-d: dominant hand; Pegboard-nd: non-dominant hand; CT1: colour trails test 1; CT2: colour trails test 2



**Supplementary Table 2: Reasons for not completing neurocognitive tests at first-line failure**

	<b>Total</b>
Total Randomised	1277
Over 18 & not at 1 excluded site	1156
<b>Colour Trail 1</b>	
Number of valid tests	1067
Number of invalid tests	89
cannot read/write	51
made a mistake	10
physically not capable/ too ill	1
site problem/error	1
unable to complete	7
Vision	13
Other	1
<b>Colour Trail 2</b>	
Number of valid tests	1047
Number of invalid tests	109
cannot read/write	51
made a mistake	19
site problem/error	1
physically not capable/ too ill	6
unable to complete	13
Vision	17
Other	2
<b>Pegboard dominant</b>	
Number of valid tests	1135
Number of invalid tests	21
no reason given	1
physically not capable/ too ill	5
unable to complete	5
Vision	10
<b>Pegboard non-dominant</b>	
Number of valid tests	1130
Number of invalid tests	26
no reason given	1
physically not capable/ too ill	6
unable to complete	8
Vision	11



**Supplementary Table 3: Test times and Z-scores at first-line failure**

Test	N	Time (sec) mean±sd	Z-score mean±sd
<b>Overall score</b>	<b>1036</b>		<b>-2.95±1.74</b>
Colour trail 1	1067	102±50	-3.72±2.37
Colour trail 2	1047	189±85	-2.73±2.16
Mean pegboard	1129		-2.63±2.20
Pegboard dominant	1135	93±38	-2.99±2.48
Pegboard non-dominant	1130	100±45	-2.29±2.22

Z-scores were truncated at -8 before calculating ~~z-scores~~ means and then taking the mean of colours trails 1 and 2 z-scores and the mean pegboard z-score to form an overall composite z-score



**Supplementary Table 4: Sensitivity analysis - complete cases multivariable risk factors at first-line failure**

Characteristic	Adjusted Difference in NPZ-3 score (95% CI) (N=983)	P value
Age per 10 year older	-0.23 (-0.35, -0.12)	<0.0001
Weight per 10kg heavier	+0.13 (0.03, +0.23)	0.01
Viral load at failure per doubling	-0.07 (-0.11, -0.02)	0.01
CD4 at failure per 100 cell higher	+0.05 (-0.06, +0.16)	0.38
Haemoglobin per g/dl higher	+0.16 (+0.11, +0.22)	<0.0001
Years of education per doubling	+0.21 (+0.04, +0.38)	0.01
Hours worked per week per 10 hour longer	+0.08 (+0.03, +0.13)	0.001
Household income		
≤\$50	0	0.04
\$50-\$200	+0.34 (+0.08, +0.61)	
>\$200	+0.20 (-0.17, +0.56)	
Previous CNS disease	-0.38 (-0.76, +0.01)	0.05
Fluconazole in the last 10 weeks	-0.55 (-0.99, -0.10)	0.01
Dapsone in the last 10 weeks	+0.62 (-0.04, +1.27)	0.07

Also adjusted for Centre  $p < 0.0001$ . Multivariable linear regression based on complete cases, and allowing non-linearity using fractional polynomials. Factors selected based on backwards elimination from all Table 1 factors with  $p < 0.2$  (exit  $p = 0.1$ ),



**Supplementary Table 5a: Sensitivity analysis - African American age adjusted colour trail z-scores**

Test	N	Z-score mean±sd
<b>Overall score</b>	<b>888</b>	<b>-3.13 ±1.8</b>
Colour trail 1	914	-4.38±3.8
Colour trail 2	897	-3.48±3.2

African American Age adjusted norms were limited to those ages between 20 and 50.

**Supplementary Table 5b: Sensitivity analysis- African American age adjusted colour trail z-scores multivariable risk factors at first-line failure**

Characteristic	Adjusted Difference in NPZ- 3 score (95% CI) (N=973)	P value
Age per 10 year older	-0.09 (-0.25, +0.06)	0.25
Weight per 10kg heavier	+0.09 (-0.01, +0.19)	0.09
Viral load at failure per doubling	-0.08 (-0.13, -0.03)	0.002
CD4 at failure per 100 cell higher	+0.09 (-0.02, +0.20)	0.10
Haemoglobin per g/dl higher	+0.16 (+0.11, +0.21)	<0.0001
Years of education per doubling	+0.77 (+0.63, +0.90)	<0.0001
Hours worked per week per 10 hour longer	+0.08 (+0.03, +0.12)	0.001
Household income		
≤\$50	0	
\$50-\$200	+0.43 (+0.15, +0.71)	
>\$200	+0.48 (+0.09, +0.86)	0.004
Previous CNS disease	-0.69 (-1.09, -0.29)	0.001
Fluconazole in the last 10 weeks	-0.42 (-0.82, -0.03)	0.04
Dapsone in the last 10 weeks	+0.33 (-0.33, +0.99)	0.33

Adjusted for Centre p<0.0001. Multivariable linear regression based on multiple imputation and allowing non-linearity using fractional polynomials. Factors selected based on backwards elimination from all Table 1 factors with p<0.2 (exit p=0.1),



**Supplementary Table 6a: Sensitivity analysis - African American Education adjusted colour trail z-scores**

Test	N	Z-score mean±sd
<b>Overall score</b>	<b>1036</b>	<b>-3.18±1.8</b>
Colour trail 1	1067	-4.23±3.4
Colour trail 2	1047	-3.50±2.9

**Supplementary Table 6b: Sensitivity analysis- African American Education adjusted colour trail z-scores multivariable risk factors at first-line failure**

Characteristic	Adjusted Difference in NPZ- 3 score (95% CI) (N=983)	P value
Age per 10 year older	-0.55 (-0.66, -0.45)	<0.0001
Weight per 10kg heavier	+0.13 (+0.03, +0.22)	0.007
Viral load at failure per doubling	-0.07 (-0.11, -0.03)	0.002
CD4 at failure per 100 cell higher	+0.09 (-0.01, +0.19)	0.07
Haemoglobin per g/dl higher	+0.14 (+0.10, +0.19)	<0.0001
Years of education per doubling	+0.69 (+0.56, +0.81)	<0.0001
Hours worked per week per 10 hour longer	+0.09 (+0.05, +0.13)	<0.0001
Household income		
≤\$50	0	0.02
\$50-\$200	+0.34 (+0.09, +0.59)	
>\$200	+0.36 (+0.02, +0.71)	
Previous CNS disease	-0.45 (-0.80, -0.09)	0.01
Fluconazole in the last 10 weeks	-0.48 (-0.86, -0.11)	0.01
Dapsone in the last 10 weeks	+0.52 (-0.11, +1.14)	0.11

Adjusted for Centre p<0.0001. Multivariable linear regression based on multiple imputation and allowing non-linearity using fractional polynomials. Factors selected based on backwards elimination from all Table 1 factors with p<0.2 (exit p=0.1),



**Supplementary Table 7a: Sensitivity analysis – Ugandan norm z-scores**

Test	N	Z-score mean±sd
<b>Overall score</b>	<b>1036</b>	<b>-0.93±1.48</b>
Colour trail 1	1067	-1.25±2.25
Colour trail 2	1047	-1.75±2.31
Pegboard- dominant hand	1133	-0.31±1.79
Pegboard- non-dominant hand	1130	+0.07±1.79

**Supplementary Table 7b: Sensitivity analysis- Ugandan norm z-scores multivariable risk factors at first-line failure**

Characteristic	Adjusted Difference in NPZ- 3 score (95% CI) (N=1137)	P value
Age per 10 year older	-0.04 (-0.05, -0.04)	<0.0001
Weight per 10kg heavier	+0.11 (+0.04, +0.19)	0.004
Viral load at failure per doubling	-0.07 (-0.11, -0.03)	<0.0001
CD4 at failure per 100 cell higher	+0.08 (-0.01, +0.16)	0.08
Haemoglobin per g/dl higher	+0.11 (+0.07, +0.15)	<0.0001
Years of education per doubling	+0.66 (+0.55, +0.77)	<0.0001
Hours worked per week per 10 hour longer	+0.09 (+0.05, +0.12)	<0.0001
Household income		
≤\$50	0	0.04
\$50-\$200	+0.25 (+0.4, +0.46)	
>\$200	+0.27 (-0.01, +0.56)	
Previous CNS disease	-0.45 (-0.75, -0.15)	0.003
Fluconazole in the last 10 weeks	-0.32 (-0.64, 0.00)	0.05
Dapsone in the last 10 weeks	+0.50 (-0.02, +1.02)	0.06

Adjusted for Centre p<0.0001. Multivariable linear regression based on multiple imputation and allowing non-linearity using fractional polynomials. Factors selected based on backwards elimination from all Table 1 factors with p<0.2 (exit p=0.1),



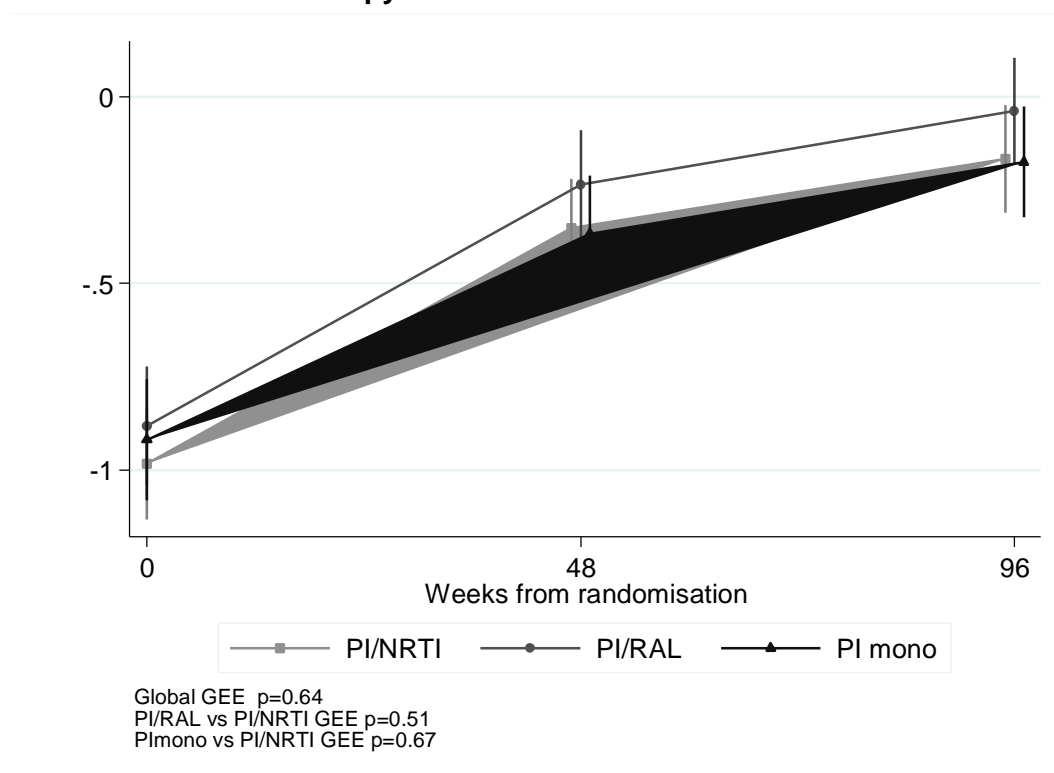
**Supplementary Table 7c: Sensitivity analysis- Ugandan norm z-scores changes in score by second-line regimen**

	PI/ NRTI N=390	PI/ RAL N=389	PI mono N=377	Global P value	PI/RAL vs PI/NRTI		PI mono vs PI/NRTI	
					Difference (95% CI)	p value	Difference (95% CI)	p value
<b>Week 0</b>								
Available	359	345	332					
mean score $\pm$ sd	-0.98 $\pm$ 1.45	-0.88 $\pm$ 1.51	-0.92 $\pm$ 1.50					
<b>Week 48</b>								
Available	324	315	304					
mean change $\pm$ se	+0.60 $\pm$ 0.05	+0.62 $\pm$ 0.05	+0.60 $\pm$ 0.06	0.96	0.02 (-0.13, +0.16)	0.84	-0.00 (-0.16, +0.15)	0.96
<b>Week 96</b>								
Available	311	306	298					
mean change $\pm$ se	+0.81 $\pm$ 0.06	+0.80 $\pm$ 0.06	+0.75 $\pm$ 0.06	0.76	-0.00 (-0.17, +0.16)	0.95	-0.06 (-0.23, +0.11)	0.51

Under 18 excluded from all analyses. P values from ANOVA and t-tests



**Supplementary Figure 1: Sensitivity analysis- Ugandan norm z-scores over time on second-line therapy**





**Supplementary Table 8: Sensitivity analysis - Including site with implementation inconsistencies multivariable risk factors at first-line failure**

Characteristic	Adjusted Difference in NPZ- 3 score (95% CI) (N=983)	P value
Age per 10 year older	-0.25 (-0.36, -0.15)	<0.0001
Weight per 10kg heavier	+0.12 (+0.02, +0.21)	0.02
Viral load at failure per doubling	-0.07 (-0.11, -0.02)	0.004
CD4 at failure per 100 cell higher	+0.10 (-0.01, +0.20)	0.08
Haemoglobin per g/dl higher	+0.16 (+0.11, +0.21)	<0.0001
Years of education per doubling	+0.40 (+0.27, +0.52)	<0.0001
Hours worked per week per 10 hour longer	+0.09 (+0.05, +0.13)	<0.0001
Household income		
≤\$50	0	0.10
\$50-\$200	+0.27 (+0.02, +0.55)	
>\$200	+0.20 (-0.15, +0.55)	
Previous CNS disease	-0.46 (-0.83, -0.09)	0.01
Fluconazole in the last 10 weeks	-0.58 (-0.96, -0.19)	0.003
Dapsone in the last 10 weeks	+0.46 (-0.15, +1.08)	0.14

Adjusted for Centre  $p < 0.0001$ . Multivariable linear regression based on multiple imputation and allowing non-linearity using fractional polynomials. Factors selected based on backwards elimination from all Table 1 factors with  $p < 0.2$  (exit  $p = 0.1$ ),



**Supplementary Table 9: Multivariable Risk factors associated with NPZ-3 score at week 48 and 96**

Characteristic	Adjusted difference in NPZ-3 score (95% CI) (N=830)	P value
Baseline NPZ-3 score	+0.57 (+0.52, +0.61)	<0.001
Weeks on second-line ART		0.02
48 weeks	0	
96 weeks	+0.38 (+0.07, +0.69)	
Age at failure per 10 year older	-0.12 (-0.20, -0.04)	0.003
Weight at current time per 10 kg heavier	+0.06 (-0.00, +0.11)	0.05
Viral load per doubling		
At failure	+0.01 (-0.02, +0.04)	0.38
At current time	+0.00 (-0.02, +0.02)	0.69
CD4 per 100 cell higher		
At failure	-0.01 (-0.07, +0.05)	0.84
Change in CD4 from failure to current time	+0.08 (+0.04, +0.13)	<0.0001
Haemoglobin at current time per g/dl higher	+0.04 (+0.00, +0.07)	0.03
Years of education at failure per doubling	+0.07 (-0.03, +0.18)	0.19
Hours worked per week at current time per 10 hour longer	+0.02 (-0.01, +0.04)	0.20
household income at current time		
≤\$50	0	0.04
\$50-\$200	+0.17 (+0.01, +0.33)	
>\$200	+0.25 (+0.05, +0.46)	
CNS disease prior to current time	-0.05 (-0.30, +0.20)	0.70
Fluconazole use prior to current time	-0.05 (-0.29, +0.19)	0.70
Dapsone use in the 10 weeks before failure	+0.11 (-0.26, +0.49)	0.55

Adjusted for Centre (p<0.0001). Model of change in NPZ-3 scores from baseline to week 48 and 96 using generalised estimating equations with an independent working correlation structure and robust variance estimators. Based on complete cases and allowing non-linearity using fractional polynomials.