No neurocognitive benefit of immediate vs delayed tesamorelin in virally suppressed people with HIV

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BACKGROUND

Neurocognitive impairment (NCI) is common in virally suppressed (VS) PWH

- CHARTER study: among (VS) PWH with a nadir CD4>200 and no confounding comorbidities, **40%** of 171 had NCI
- ACTG ALLRT study: **39%** of 3,313 VS PWH had NCI
- NCI is associated with disability independent of other factors (frailty, comorbidities)
- Increased waist circumference (WC, a surrogate for abdominal obesity / visceral adiposity) is common in PWH and a risk factor for NCI

Tesamorelin (Egrifta®, growth hormone releasing hormone)

- reduces visceral adiposity (visceral adiposity) and inflammation
- increases neurotrophic hormone IGF-1
- In animals, it stimulates brain blood flow, angiogenesis, and neurogenesis; protects against oxidative stress; improves brain glucose utilization

Objective: To determine if tesamorelin improves NC performance in virally suppressed PWH with NCI and abdominal obesity

METHODS

Eligibility

Inclusions: HIV+ males and females, 40+ years; minimal WC ≥ 95cm (males), ≥94cm or minimal waist-to-hip ratio of ≥ 0.88 (females); screening NC GDS ≥0.35; stable cART ≥12 weeks; viral load undetectable (blips OK); hemoglobin A1C ≤8.0%

Exclusions: Severe neurocognitive confound other than HIV; active substance use disorder or other major confounding conditions

Neurocognitive (NC) testing

- **Screening*** (pre-randomization): Tests of verbal learning and memory, speeded information processing (SOP), working memory, executive function, and motor functioning (HVLT-R, Digit Symbol, Symbol Search, Grooved pegboard, PASAT, Stroop)
- **Comprehensive** (weeks 0, 24, 48): Tests of basic academic skills, nonverbal learning and memory, and verbal fluency, plus additional tests of SOP, working memory, executive and motor function (WRAT-4, BVMT-R, COWA-FAS, Category Fluency, Trailmaking A/B, WAIS-III LNS, Wisconsin CST).
- **Figure 1** shows the study schema
- **Primary outcome:** change in NC from week 0-24 (sRCS)
- Continuous Summary Regression-Based Change Score (sRCS; overall NC change compared to normative expectations)

Study Treatment

- Tesamorelin (Egrifta) 1.4 mg subcutaneous injection daily for 24 weeks. Randomization ratio Immediate: Deferred = 3:2

* good concordance with Comprehensive battery

Abbreviations: NCI=neurocognitive impairment, WC=waist circumference, sRCS=summary regression change score, VA=visceral adiposity, AO=abdominal obesity, GDS-global deficit score,

Figure 3. The primary outcome did not differ for immediate versus delayed tesamorelin

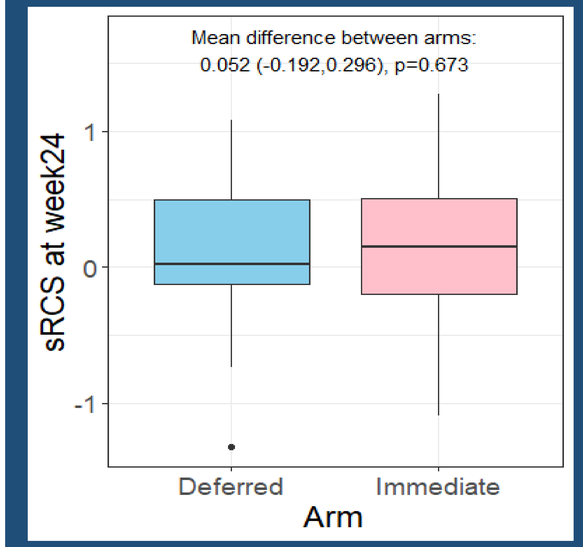
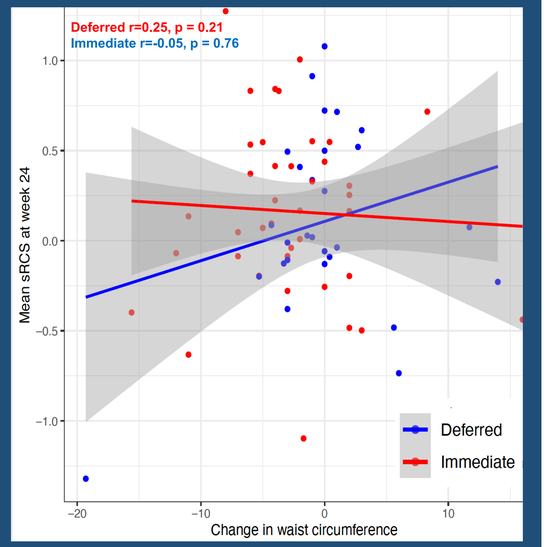
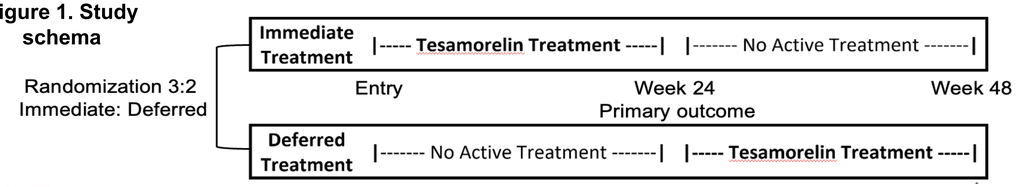


Figure 4. Correlations between change in WC and sRCS did not differ between arms



sRCS = summary regression-based change score (PMID: 21391011)

Figure 1. Study schema



RESULTS

Figure 2. CONSORT Flow Diagram

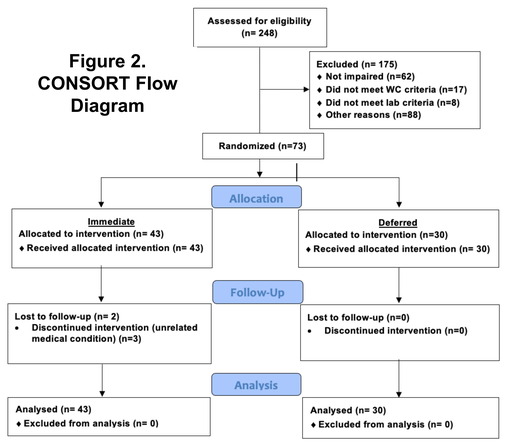


Table 1. Baseline demographic and disease characteristics by arm

	Immediate (n=30)	Delayed (n=43)	p
Demographics			
Age - mean (SD)	57.4 (10.8)	59.5 (8.5)	0.381
Sex, female - N (%)	2 (6.7%)	6 (14.0%)	0.458
Years of education - mean (SD)	14.4 (3.2)	13.9 (3.0)	0.505
Race/Ethnicity	10 (33.3%)	16 (37.2%)	0.884
Black	3 (10.0%)	2 (4.7%)	
Non-Hispanic White	17 (56.7%)	24 (55.8%)	
Other	0 (0.0%)	1 (2.3%)	
HIV Disease Characteristics			
Nadir CD4+*	187 [52.8;382]	200 [146;297]	0.560
Current CD4+*	763 [478;894]	651 [496;935]	0.909

*median, IQR CD4+ T lymphocytes/ul

RESULTS

- **Figure 2** is the CONSORT flow diagram
- **Table 1** shows no significant demographic or HIV disease differences between the treatment allocation arms
- **Table 2** shows baseline and 24-week change values for the primary outcome and WC. The arms did not differ significantly on these measures
- **Figure 3** shows the primary outcome. Change in cognitive performance (sRCS) over 24 weeks did not differ between arms (see **Table 2** for detailed statistics)
  - No difference between arms in a sensitivity analysis sRCS at week 24 among those impaired at baseline (GDS ≥ 0.50 (N=56): (p=0.605)
- WC decreased more in the Immediate arm
- Change in WC did not correlate with change in sRCS
- Median self-reported adherence 94.6% in those on study drug

Table 2. Baseline and change values for key study measures

	Immediate	Deferred	p
Δ NC performance (GDS)	0.939 (0.717, 1.614)	0.861 (0.653, 1.069)	0.619
Baseline WC (cm)	111 (108, 114)	110 (106, 114)	0.655
Δ NC performance (sRCS)*	0.155 (0.001, 0.309)	0.103 (-0.095, 0.301)	0.673
versus no Δ (within group)	p=0.048	p=0.295	--
Δ WC (cm)	-2.78 (-4.57, -0.986)	-0.187 (-2.42, 2.04)	0. 067
versus no Δ (within group)	0.003	0.866	--
*primary outcome			

CONCLUSIONS

- Despite expected reductions in WC, a surrogate for abdominal obesity (AO), tesamorelin did not significantly improve NCI in VS PWH compared to deferred initiation
  - Some evidence of benefit in the immediate arm, but not significantly greater than deferred
- Findings do not support the hypothesis that AO contributes significantly to NCI in PWH
- Underpowered
- Unblinded, no concurrent placebo comparison

FUTURE DIRECTIONS

- Possible future studies with larger numbers of participants and longer follow-up duration
- Analyses of quality of life, depression, ADLs underway
- Analyses of neuroimaging (brain and abdomen structural MRI, magnetic resonance spectroscopy), IGF-1 levels, other biomarkers, and CSF studies underway

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