REVIEW ARTICLE

Adjuvant therapies for HIV-associated neurocognitive disorders

Jennifer L. McGuire^{1,2,3,}, Jeffrey S. Barrett⁴, Heather E. Vezina⁴, Sergei Spitsin⁵ & Steven D. Douglas^{5,6,7}

¹Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

²Department of Neurology, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

³Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

⁴Laboratory for Applied PK/PD, Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania ⁵The Children's Hospital of Philadelphia Research Institute, Philadelphia, Pennsylvania

⁶Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

⁷Department of Pediatrics, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Correspondence

Jennifer L. McGuire, Division of Neurology, The Children's Hospital of Philadelphia, 34th St and Civic Center Blvd, Philadelphia, PA 19104. Tel: 1-215-590-1719; Fax: 215-590-1771; E-mail: mcguirej@email.chop.edu

Funding Information

Dr. McGuire's training and research are supported by the National Institutes of Health (K12-NS049453) and pilot awards from MH097488 and UL1TR000003. Dr. Barrett's research is supported by the National Institutes of Health (U01-MH090325, U54-HD071598, HHSN275201000003I, R01-FD004095-01A1). Dr. Spitsin's research is supported by the National Institutes of Health (U01-MH090325, R01-MH049981, R21-Al108298 [to S. D. D.]). Dr. Douglas's research is supported by the National Institutes of Health (R01-MH049981, 1U01-MH090325, UM1-Al69467, R21-Al108298, UO1HD040481, P30-MH097488).

Received: 17 July 2014; Revised: 15 September 2014; Accepted: 16 September 2014

Annals of Clinical and Translational Neurology 2014; 1(11): 938–952

doi: 10.1002/acn3.131

Introduction

Human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) is a common manifestation of HIV affecting nearly 50% of infected individuals in the combined antiretroviral therapy (cART) era.¹ While HAND is a heterogeneous disorder comprised various degrees of cognitive impairment, the presence of any type of HAND contributes to HIV-associated medical and social burden. Specifically, HAND independently predicts worsened HIV treatment adherence, is associated with unemployment and functional disability² exposing affected individuals to financial errors and unsafe situations³, and predicts non-CNS (central

938 © 2014 The Authors. Annals of Clinical and Translational Neurology published by Wiley Periodicals, Inc on behalf of American Neurological Association. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Abstract

Objective: HIV-associated neurocognitive disorder (HAND) is a frequent and heterogeneous complication of HIV, affecting nearly 50% of infected individuals in the combined antiretroviral therapy (cART) era. This is a particularly devastating statistic because the diagnosis of HAND confers an increased risk of HIV-associated morbidity and mortality in affected patients. While cART is helpful in the treatment of the more severe forms of HAND, there is a therapeutic gap in the milder forms of HAND, where cART is less effective. Multiple adjuvant therapies with various mechanisms of action have been studied (N-methyl D-aspartate [NMDA]-receptor antagonists, MAO-B inhibitors, tetracycline-class antibiotics, and others), but none have shown a clear positive effect in HAND. While this lack of efficacy may be because the appropriate therapeutic targets have not yet been determined, we aimed to discuss that study results may also influenced by clinical trial design. Methods: This report is a systematic review of clinical trials of adjuvant therapies for HAND performed from January 1996 through June 2014. Results: Possible drawbacks in study design, including lack of standardized case definitions, poorly defined target populations, inappropriate dose selection and measurable outcomes, and brief study durations may have masked true underlying mechanistic effects of previously investigated adjuvant therapies for HAND in specific patient populations. Conclusions: A proposal for streamlining and maximizing the likelihood of success in future clinical studies using a "learning and confirming" investigational paradigm, incorporating stronger adaptive Phase I/II study designs, computerized modeling, and population/goal of treatment-specific Phase III clinical trials is presented.

nervous system) peripheral morbidity and overall mortality.^{3–5}

To date, the only therapy that has had a significant impact on the clinical course of HAND is cART. However, while cART reduced the incidence⁶ of severe cases of HAND (HIV-associated dementia [HAD]) and ameliorated some cognitive difficulties,^{7,8} it has not had a clearly beneficial effect on milder forms of HAND, including mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI), which are now more prevalent than HAD¹. This "therapeutic gap" probably occurs because these disorders are not only a consequence of the direct viral effects targeted by cART, but are also (and perhaps primarily) mediated by a complex neuropathophysiology that indirectly involves immune dysregulation, neuroinflammation, and neuronal excitotoxicity⁹⁻¹¹. A therapy that targets these indirect effects is therefore needed.

Multiple medication classes (MAO-B inhibitors, tetracycline-class antibiotics, N-methyl D-aspartate [NMDA] antagonists, and others) have been examined as possible adjuvant therapies to cART for HAND. While several studies have demonstrated some element of possible neuroprotection based on secondary endpoints such as proton MR spectroscopy,^{12–14} no clinical trial has demonstrated a clear positive effect on cognitive function¹⁵, so no adjuvant therapies are recommended for routine clinical use¹⁶. While this lack of significant treatment effect may be because the appropriate therapeutic targets of HAND have not yet been determined, it may also have been influenced by clinical trial design, which is heterogeneous across studies and subject to real-world constraints of cost and time. Here, we review clinical trials of adjuvant therapies in the cART era, and examine study design components that may have influenced the assessment of efficacy and generalizability of results.

Materials and Methods

To examine critical design elements of recently published adjuvant therapy trials for HAND, a PubMed search for articles published between 1 January 1996 and 11 June 2014 was performed using the keywords (["cognitive impairment" OR "neurocognitive" OR "cognitive-motor impairment"] AND "HIV" AND ["trial" OR "pilot"]). One hundred and twenty-five publications were identified. Of those 125, 107 observational and preclinical studies, and trials examining nonpharmacologic interventions, cART alone, and restricted subgroups of HIV-infected patients with comorbidities that may contribute to cognitive dysfunction (depression, fatigue, and drug abuse) were excluded. Eighteen studies therefore comprised the study dataset for subsequent analysis.

Results

The 18 studies included in this review are summarized in Table 1. Primary trials are listed chronologically by candidate therapy and clustered with associated openlabel extension studies or secondary analyses. Each primary study is also assigned a character value (e.g., a.) and each extension study or secondary analysis is assigned a character/numeric value (e.g., a1) for ease of referencing throughout the review.

Since the advent of cART in 1996, a total of 12 different adjuvant therapies to cART have been studied, including rivastigmine (acetylcholinesterase inhibitor), minocycline (tetracycline-class antibiotic), memantine (NMDA-receptor antagonist), selegiline (MAO-B inhibitor), thioctic acid (α-lipoic acid), valproic acid (HDAC inhibitor, GABAergic effects), lithium (unknown mechanism), CPI-1189 (tumor necrosis factor α blocker), Peptide T (d-ala-peptide-T-amide, reportedly blocks gp120 binding to brain tissue and protects neurons from direct toxic effects of gp120), lexipafant (platelet-activating factor receptor antagonist), and OPC-14117 (free radical scavenger). None of these trials demonstrated obvious direct clinical efficacy in HAND, and none of these investigational therapeutics are in current clinical use, although many of these studies were only powered to assess safety and tolerability (f, g, h, j, k, m, n). Fourteen trials enrolled less than 100 subjects; no trial enrolled more than 215 subjects. Comorbid conditions that may contribute to risk of cognitive decline were rarely constrained by enrollment criteria and not always reported. Only one primary study and its substudy clearly described a dosage regimen based on relevant pharmacodynamic indices in this population (l, l1). Finally, no trial that met our search criteria was continued for more than 6 months, other than one open-label extension study (d1).

Discussion

While trial results of adjuvant therapies for HAND have not been promising to date, there are a variety of design elements that could be improved upon affording candidate therapies with relevant mechanisms of action and promising preclinical data better chances to succeed. Components of trial design to target in order to optimize outcomes are outlined in Table 2.

Case definitions

The Memorial Sloan Kettering (MSK) staging scale for HAND was first developed in 1988 to establish a threshold for diagnosis of the then coined term, AIDS Dementia Complex (ADC).¹⁷ However, ADC is not specific for the

iniai arita designi a.Rivastigmine (Simioni et al.) ²⁵ Randomized, double-blind, niacueho-				DOSE SELECTION			Church r drugshan
a Rivastigmine (Simioni et al.) ²⁵ Randomized, double-blind, nlareho-			,				Study duration
(Simioni et al.) ²⁵ Randomized, double-blind,	Frascati criteria	HAND: MND or HAD	Assess safety and	Based on studies in	20-week change	HAND: 100% MND	20 + 6 weeks
Randomized, double-blind, nlaceho-		Age: not specified	efficacy to treat	Alzheimer's Disease;	in absolute	Sex: 71% male	wash out +
double-blind, nlareho-		ART: not specified, but all enrolled on ART.	HAND in a cohort	1.5 mg/day	Alzheimer's	Age (mean \pm SD): 55.1 \pm 9.7 years	20-week
nlacaho-		CD4 count: not specified	of aviremic HIV-	increased every	Disease	Race/Ethnicity: not reported	crossover
000000		VL: undetectable VL in plasma (<20 copies/mL	infected subjects.	2 weeks to 3, 4.5,	Assessment	Education (mean \pm SD): 12.6 \pm 2.8 cells/mm ³	
controlled		for 3 months) and CSF (<200 copies/mL)		6, 9, and 12 mg/	Scale-Cognitive	Duration HIV+ (mean \pm SD): 14.2 \pm 7.1 years	
crossover				day	subscale	CD4 count (mean \pm SD): 669 \pm 222 cells/mm ³	
study					(ADAS-Cog)	CD4 nadir (mean \pm SD): 177 \pm 100 cells/mm ³	
<i>n</i> = 17						Plasma VL: 100% undetectable	
						Injection drug use: active use excluded	
						Karnofsky Score: not reported	
b.Minocycline	MSK staging	HAND: ADC stage 0.5 or 1, with	Assess the efficacy,	Not discussed	24-week change in	HAND: 99/1 % ADC 0.5/1	24 weeks
(Nakasujja		International HIV Dementia Scale <10	tolerability, and		absolute	Sex: 10% male	RCT + 24
et al.) ²⁷		Age: 18–65 years	safety of		neurocognitive	Age: 18–65 years	weeks open
Randomized,		ART: naïve	minocycline for		composite z-score	Race/Ethnicity: 100% black, Ugandan	label
double-blind,		CD4 count: 250–350	the treatment of		measured by	Education: 79% with ≤ 10 years	
placebo-		VL: not specified	HAND in Ugandan		the Uganda	Duration HIV+: not reported	
controlled			ART-naïve		Neuropsych Test	CD4 count (mean \pm SD): 320 \pm 52 cells/mm^3	
study (NS32228)			subjects.		Battery ¹ Summary	CD4 nadir: not reported	
<i>n</i> = 73					Measure	Log10 Plasma VL: 4.50 \pm 0.73 copies/mL	
						Injection drug use: not reported	
						Karnofsky Score: 100% with ≥80	
c.Minocycline	MSK staging	HAND: Cognitive impairment	Assess safety,	Not discussed	24-week change	HAND: 4/51/38/7% ADC 0/0.5/1/2	24 weeks
(Sacktor et al.) ²⁸	Cognitive	with progressive decline, stratified	tolerability, and		in absolute	Sex: 89% male	
Randomized,	impairment: ≥1 SD	based on subjective versus objective	efficacy for the		NPZ-8 ² score	Age (mean \pm SD): 51 \pm 7 years	
double-blind,	below norm on	criteria.	treatment of			Race/Ethnicity: 55/45% white/black	
placebo-	≥3 tests, or ≥2 SD	Ages: 18–65 years	HIV-associated			Education (mean \pm SD): 14 \pm 3 years	
controlled study	below norm on	ART: stable regimen for ≥6 weeks	cognitive			Duration HIV+: not reported	
(ACTG)	1 test + ≥1 SD	CD4 count: not specified	impairment.			CD4 count (mean \pm SD): 543 \pm 283 cells/mm ³	
<i>n</i> = 107	below norm on	VL: stratified based on CSF				CD4 nadir (mean \pm SD): 270 \pm 254 cells/mm^3	
	a 2nd test	VL (<30 copies/mL, ≥30 copies/mL, not				Plasma VL <30 copies/mL (mean): 86%	
		measured)				Injection drug use: 76% never use,	
						active use excluded	
						Karnofsky Score: not reported	
d.Memantine	MSK staging	HAND: ADC stage ≥1, stratified on ADC stage.	Assess the safety	Not discussed	16-week change	HAND: 76% ADC 1	16 weeks
(Schifitto et al.) ¹²		Ages: not specified	and efficacy of		in percent NPZ8 ²	Sex: 90% male	
Randomized,		ART: stable regimen for ≥ 6 weeks,	memantine as			Age (median [95% Cl]): 43 (31–63)	
double-blind,		stratified on zidovudine use	treatment for			Race/Ethnicity: 72% white	
placebo-controlled		(never, previous, current)	HIV-associated			Education: 34% <pre><12</pre> years	

Table 1. Clinical trials for adjuvant therapy of HAND since 1 January 1996.

(Continued)

Trial and design	Case definitions	Target population (key inclusion and exclusion criteria)	Objective of trial	Dose selection	Primary outcome	Selected covariates and confounders	Study duration
study (ACTG 301) n = 140		CD4 count: not specified VL: not specified	cognitive impairment.			Duration HIV+: not reported CD4 count (median [95% CI]): 274 (4–1496) cells/mm ³ CD4 nadir: not reported Plasma VL (median): 112 copies/mL Injection drug use: 82% never use Kamofsky Score: not reported	
d1.Memantine (Zhao et al.) ²⁹ Randomized, double-blind, placebo- controlled study, open-label extension phase of above ¹² (ACTG 301) n = 99	MSK staging	HAND: ADC stage ≥1 Ages: not specified ART: stable regimen for ≥6 weeks CD4 count: not specified VL: not specified	Provide further safety and efficacy information on long-term memantine use as adjuvant therapy in HAND.	Not discussed	12-week absolute change in NP28 ² score following 20 week original randomized trial.	HAND: not reported Sex: 90% male Age (median [95% CI]): 43 (37-49) Race/Ethnicity: 75/10% white/black Education: 30% ≤12 years Duration HIV+: not reported CD4 count (median [95% CI]): 316 (189-473) cells/mm ³ CD4 nadir: not reported Plasma VL: not reported Injection drug use: 84% never use, no active Kanrofsky Score (median [IQR]): 80 (70, 90)	Up to 60 weeks open-label extension.
e.Selegiline Transdermal System (STS) (Schriftto et al.) ³⁰ Randomized placebo-controlled study (ACTG 5090) n = 128	MSK staging Cognitive impairment: ≥1 SD below norm on below norm on 1 test.	HAND: Any cognitive impairment. Stratified ADC stage (0.5 vs. ≥1). Ages: not specified ART: stable regimen, duration/type not specified CD4 count: not specified VL: stratified on VL (<200 copies/mL, ≥200 copies/mL)	Assess satety, tolerability, and efficacy of STS for the treatment of HAND.	Not discussed	24-week change in absolute NP26 ³	HAND: 34/62% ADC 0.5/1–2 Sex: 88% male Age (median): 45 years Race/Ethnicity: 51/36% white/black Education (median (IQR)): 13 (12, 16) Duration HIV+ (median (IQR)): 13 (12, 16) Duration HIV+ (median (IQR)): 13 (12, 16) 2 (3 (5, 14.7) CD4 count (median (IQR)): 422 (261, 691) cells/mm ³ CD4 nadir: not reported Plasma VL: 35% with ~50 copies/mL Injection drug use: not reported Karnofsky Score: 77% with ~80	24 weeks
e1.Selegiline (STS) (Schiftto et al.) ³¹ Substudy of above randomized placebo-controlled study ³⁰ (ACTG 5090) n = 62	MSK staging Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test.	HAND: Any cognitive impairment. Stratified ADC stage (0.5 vs. ≥1). Ages: not specified ART: stable regimen, duration/type not specified CD4 count: not specified VL: stratified on VL (<200 copies/mL, ≥200 copies/mL)	Assess effectiveness of STS in reversing HIV-induced metabolic brain injury (measured by magnetic resonance spectroscopy, MRS) and in	Not discussed	12- and 24-week changes in MRS metabolite ratios	HAND: 40/52/8% ADC 0.5/1/2 Sex: 87% male Age (median): 46 years Race/Ethnicity: 39/55% white/black Education (median): 12 Duration HIV+: not reported CD4 count (median): 361–384 cells/mm ³ across treatment groups CD4 nadir: not reported	24 weeks

Table 1. Continued.

Trial and design	Case definitions	Target population (key inclusion and exclusion criteria)	Objective of trial	Dose selection	Primary outcome	Selected covariates and confounders	Study duration
			decreasing oxidative stress (measured by CSF [protein carbonyl])			Plasma VL: 77% with <50 copies/mL Injection drug use: not reported Karnofsky Score: 69% with ≥80	
e2.Selegiline (STS) (Evans et al.) ³²	MSK staging Cognitive	HAND: Any cognitive impairment. Stratified ADC	Provide long-term safety (primary	Not discussed	24-week change (open-label	HAND: not reported Sex: 86% male	24 week open- label extension
Open-label treatment phase of above	impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD	stage (0.5 vs. ≥1). Ages: not specified ART: stable regimen, duration/type not	aim) and efficacy (secondary aim) of STS for the		period only) in absolute NPZ6 ³ .	Age (median [IQR]): 46 (42, 52) years Race/Ethnicity: 5.1/33% white/black Education (median): not reported	
randomized placebo-controlled study ³⁰ (ACTG 5090) n=86	below norm on 1 test.	specified CD4 count: not specified VL: stratified on VL (<200 copies/mL, ≥200 copies/mL)	treatment of HAND.			Duration HIV+: not reported CD4 count (median): 414 cells/mm³ CD4 nadir: not reported Plasma VL: 36% with <50 copies/mL Injection drug use: not reported Kannofsky Score: 80% with ≥80	
f.Seleguine (STS) (Sacktor et al.) ³³ Randomized, double-blind, placebo-controlled pilot study	MSK staging Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on	HAND: Any cognitive impairment. Ages: ≥18 years ART: stable regimen for ≥6 weeks CD4 count: not specified ; VL: not specified	Obtain preliminary data to assess safety, tolerability, and impact of transdermal selegiline on HANN	Based on in vitro study of oral selegiline demonstrating synthesis of neuronal	Whether or not the subjected completed the study on the original dose of medication.	HAND: 57/36/7% ADC 0.5/1/2–3 Sex: 71% male Age (mean): 42 years Race/Ethnicity: 57/43% white/black Education (mean): 12.2 years Durarion HV4. (mean): 77 years	10 weeks
n = 14 g.Deprenyl (selegiline) and thioctic acid (The Dana Consortium 1998) ³⁴	I test MSK staging Cognitive impairment: ≥1 SD below norm on	HAND: Any cognitive impairment. Ages: ≥18 years ART: stable regimen for ≥6 weeks	HAND. Assess safety, tolerability, and impact of deprenyl and	antiapoprotic genes in injured neurons. Deprenyl dose chosen to incompletely inhibit	Whether or not the subjected completed the study on the	Duration HU+ (mean): 5.7 years CD4 count (mean): 294 cells/mm ³ CD4 nadir: not reported Plasma VL: not reported Injection drug use: not reported Kannofsky Score (mean): 81 HAND: 8/61/25/6% ADC 0/0:5/1/2–3 Sex: 72% male Age (mean): 41.2 years	10 weeks
Randomized, double-blind, placebo- controlled, 2 × 2 factorial design n=36	≥2 tests, or ≥2 SD below norm on 1 test.	CD4 count: not specified VL: not specified	thioctic acid on HAND	monoamine oxidase type B. Thioctic acid dose selection not discussed.	original dose of medication.	Race/Ethnicity: 55/33% white/black Education (mean): 13.4 years Duration HIV+ (mean): 5.7 years CD4 count (mean): 208 cells/mm ³ CD4 nadir: not reported Plasma VL: not reported Injection drug use: not reported Karnofsky Score: not reported	

(Continued)

Table 1. Continued.

942

© 2014 The Authors. Annals of Clinical and Translational Neurology published by Wiley Periodicals, Inc on behalf of American Neurological Association.

Type Type <th< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></th<>								
of King Cognitive invaluence: HADD: Ion specified Adds: Ion specified Ion specified Adds: Ion specified Adds: Ion specified Adds: Ion specified Adds: Ion specified Ion sp	Trial and design	Case definitions	Target population (key inclusion and exclusion criteria)	Objective of trial	Dose selection	Primary outcome	Selected covariates and confounders	Study duration
(4)(b) Coprile impairment HaMD not specified Asses safery and Not decisioned Dowes (a) 21.5 below com Sim of specified Vist and epicer Dowes Uniteraction (b) 10.1 below com Sim or specified Vist and epicer Dowes Dowes (b) 11.0 below com Sim or specified Commander Sim of specified Dowes Dowes (c) 11.0 below com Sim or specified Commander Sim of specified Dowes Dowes (c) Dowes Sim or specified Commander Sim of specified Dowes Dowes (c) Dowes Dowes Dowes Dowes Dowes (c) Dowes <t< th=""><th></th><th></th><th></th><th>,</th><th></th><th></th><th></th><th>,</th></t<>				,				,
(a) ¹¹ 2:15 Debonrom Stront gotied Denailing of the non-non-non-specified Denailing of the non-non-non-specified Denailing of the non-non-non-non-perified Denailing of the non-non-non-non-perified Denailing of the non-non-non-non-perified Denailing of the non-non-non-non-non-non-non-non-non-non	h.Valproic acid (VPA)	Cognitive impairment:	HAND: not specified.	Assess safety and	Not discussed	10-week	HAND: 73/27% impaired/	10 weeks
dit or 2 tests, or 2 20 test minimer is minimer is minimer is below normen and a minimer is effect on a first minimer is and pations. test memory is effect on a metabolism test metabolism test memory is effect on a metabolism test memory is effect on a metabolism test metabolism test metabolism test memory is effect on a metabolism test metabolism <thtest metabolism<="" th=""> <thtest metabolism<="" th=""> <t< td=""><td>(Schifitto et al.)¹³</td><td>≥1 SD below norm</td><td>Stratified on impairment</td><td>tolerability of</td><td></td><td>difference in</td><td>unimpaired</td><td></td></t<></thtest></thtest>	(Schifitto et al.) ¹³	≥1 SD below norm	Stratified on impairment	tolerability of		difference in	unimpaired	
di blow norm of tra. App: not specified of cut or specified Cd cut cut cut or specified Cd cut	Ran domized,	on ≥ 2 tests, or ≥ 2 SD	(unimpaired vs.impaired)	VPA and explore		tolerability	Sex: 77% male	
1 bit. Aff. not specified copilitie and pleecio. plot 1 curr. tor specified bein metabolism and pleecio. 1 curr. V.: not specified bein metabolism and pleecio. 1 curr. V.: not specified bein metabolism bein metabolism 1 curr. ANI criteria HAID. MCM0 or HAD Determine the Not discussed 12, week 1 curr. ARI criteria HAID. MCM0 or HAD Determine the Not discussed 12, week 1 1 curr. Copilitie curr. ARI criteria network difference in 4000 defect 1 curr. Copilitie not correct. copilitie performance of proference performance of copilitie 1 curr. Copilitie not correct. Not discussed not correct. 10, week 1 curr. Copilitie Not copilitie performance of copilitie score (COS) 1 curr. Not copilitie not copilitie performance of copilitie score (COS) 1 curr. Not copilitie not copilitie performance of copilitie score (COS) 1 curr. Not copilitie not copilitie performance of copilitie score (COS) 1 curr. Not copilitie not copiliti	double-blind,	below norm on	Ages: not specified	its effect on		between VPA	Age (mean): 43.5 years	
plot Cot court: not specified performance and brain metabolism AM criteria H-mot specified brain metabolism 14.a) ¹³ AM criteria H-mot specified brain metabolism 14.a) ¹³ AM criteria H-mot specified brain metabolism 14.a) ¹⁴ AM criteria H-mot specified brain metabolism 10.a AM criteria AM criteria brain metabolism 10.a Col count: solo ouldy tip preferred brain metabolism score (CDS ¹) 10.a Col count: solo ouldy tip preferred brain metabolism score (CDS ²) 10.a Col count: solo ouldy tip preferred brain metabolism score (CDS ²) 10.a To count: solo ouldy tip preferred brain count: solo ouldy tip preferred score (CDS ²) 10.a To construct brain count count score (CDS ²) score (CDS ²) 10.a To construct brain count score (CDS ²) score ould count 10.a	placebo-	1 test.	ART: not specified	cognitive		and placebo.	Race/Ethnicity: 45/55% white/black	
V: not specified Determine the N: not specified Determine the N: not specified N: not specified AM criteria HAKD: MCMD or HAD Determine the Refers of bio: Not discussed 12 welk ARI criteria HAKD: MCMD or HAD Determine the Refers of bio: Not discussed 12 welk ARI stable regimen for >12 welks does ont Lion addition addition C45 count: Si00 diskl, preferred but nut cut required. polad refrict N: -400 or specified nut certained 2 welk 1 Cognitive nut certained 12 welk 1 N: -400 or specified nut certained 2 welk 1 N: -400 or specified nut certained 12 welk 1 Cognitive impairment mucroscomise 10 or discosed 20 or discosed Stable regiment bit nut certained 10 or discosed 10 or discosed ARI: stable regiment for 28 weeks 10 or discosed 10 or discosed 10 or discosed 10 or discosed 10 or discosed 10 or discosed	controlled pilot		CD4 count: not specified	performance and			Education (mean): 12 years	
AMI cireia HAID: MCH0 or HAD Determine the Not discussed 12-week e1a1 ³⁰ Age: 18-55 years effects of low- Not discussed 12-week pilot Age: 18-55 years effects of low- Not discussed 12-week pilot C49 court: -500 celepid perferred premons/or of low- Not discussed 12-week not required. Determine the Not discussed 12-week 1 not contraction C04 court: -500 celepid perferred premons/or of low- Not discussed 12-week not required. Determinance of reuropsychological poblid definit not required. Not HVA-sasciated volt HVA-sasciated 1 not required. Perfect on cognitive neurocognitive 1 not required. Aff: stable Aff: stable 0 1 not required. Aff: stable Aff: stable 1 0 not required. Aff: stable Aff: stable 1 0 not required. Aff: stable 1 0 1 not required. Aff: stable 1 0 1 not required. Aff: stable 1 0 1 non retst. Aff: stable 1 <td< td=""><td>study</td><td></td><td>VL: not specified</td><td>brain metabolism</td><td></td><td></td><td>Duration HIV+ (mean): 9.4 years</td><td></td></td<>	study		VL: not specified	brain metabolism			Duration HIV+ (mean): 9.4 years	
AM criteria MAD: MCMO or HAD et al. ³⁷ AM criteria MAD: MCMO or HAD et al. ³⁷ AM criteria MAD: MCMO or HAD et al. 2 week, and a construction of the memory of the	<i>n</i> = 22						CD4 count (mean): 434 cells/mm ³	
AM criteria HAND: MCMO or HAD Determine the Nor discussed 12-week a defects of low- at al. ³⁴ AM criteria HAND: MCMO or HAD Determine the Nor discussed 12-week a defects of low- Age: 16-65 years defects of low- Age: 16-65 years defect and the neuropsychological address of a defect and address of a defect address of addr							CD4 nadir: not reported	
Adv citeria HAVD: MCM0 or HA0 Determine the effects of low- plot Not discussed 12-week - et al. ³⁷ Age: 18-65 yaars effects of low- differencein Not discussed 12-week - plot Age: 18-65 yaars effects of low- biot Ade core call (in on- biot - - - plot CDA count: -500 cell/ul, preferred biot -							Plasma VL: 45% with <50 copies/mL	
AN criteria HAUD: MCMD or HAD Determine the Not discussed 12-week 1 - ART: stable regimen for 212 weeks of effects of low: ART: stable regimen for 212 weeks of status in the neuropsychological activity about the transmore of the neuropsychological but not required. ART: stable regimen, in planta performance of status of the neuropsychological but not required. ART: stable regimen, in planta performance of score (GDS ⁵) activity of the neuropsychological but not required. ART: stable regiment in the neuropsychological but not required. ART: stable regiment in the neuropsychological but not required. ART: stable regiment in the neuropsychological but not required in the neuroscipation of neuroscipation in the neuroscipation of impairment. ART: stable regiment for 28 weeks and explore its inpairment in norm on 1 test. ART: stable regiment for 28 weeks in the neuromony of the norm of the norm in the neuromony in the norm of the neuromony in the norm of the neuromany in the norm of the norm of the neuromany in							Injection drug use: not reported	
AN criteria HAID: MCAP or HAD et al. ³⁷ And criteria HAID: MCAP or HAD et al. ³⁷ And criteria HAID: MCAP or HAD Ang: He S5 years desire of low- Ang: He S5 years desire does desired of low- and CSF preferred but in plasma people diagnosed but not required. UC-600 copiesmi in plasma people diagnosed and CSF preferred but in plasma in the inplasment. (1) ⁴ Impairment: 21 Age: not specified and cSF preferred but introdom and explore its and							Karnofsky Score (mean): 90	
et al.) ³⁶ Age: 18-65 years effects of low- plot - C. Add. stable regimen for 212 weeks doe oral Lion absolue but not required - consisplut preferred - performance of vice 400 copie/mL in plasma - people diagnosed - score (GDS ⁵) vice 400 copie/mL in plasma - with NiV-assolated - score (GDS ⁵) vice 400 copie/mL in plasma - with NiV-assolated - score (GDS ⁵) and CS preferred but - neurocopinitie - neurocopinitie - neurocopinitie - neurocopinitie - neurocopinitie - not required - not above - not specified - nor and comine - not required - nor or 25 D below - Ni: not specified - nor not rest	i.Lithium (Li)	AAN criteria	HAND: MCMD or HAD	Determine the	Not discussed	12-week	HAND: AAN categories not reported.	12 weeks
 Aff. stable regimen for ≥12 weeks does oral Li on absolute protonogration of the score (GDS⁴) preferred in the uncopychological preferred but not required. CO4 court: = 500 cellyful, preferred but not cequired. VL: = 400 creative performance of nucrosychological and CSF preferred but with HVA-associated not required. Coprilive hAND: Any cognitive impairment impairment. Coprilive hAND: Any cognitive impairment and compared and CSF preferred but not required. Coprilive hAND: Any cognitive impairment and compared and CSF preferred but not required. Coprilive hAND: Any cognitive impairment at non-compared and CSF preferred but not required. Coprilive hAND: Any cognitive impairment at non-compared and compare in an and compare is a non-compare in a second compare in the impairment. Coprilive hAND: Any cognitive impairment at non-compare in a non-compare in a second compare in a second compare is impairment. Coprilive hAND: Any cognitive impairment at non-compare in a second compare is impairment. Coprilive hAND: Any cognitive impairment at non-compare is impairment. Coprilive hAND: Any cognitive impairment at non-compare is impairment. Coprilive hAND: AND: AND: AND: AND: AND: AND: AND:	(Letendre et al.) ³⁵		Age: 18–65 years	effects of low-		difference in	Mean $GDS = 0.74$	
plot C04 count: -500 cells/ul prétend neuropsychologial global déficit but not required. but not required. performance of score (GDS ⁵) v1: -400 copis/mit in plasma people diagnosed score (GDS ⁵) and CS prefered but neurosophitee score (GDS ⁵) not required. neurosophitee neurosophitee neurosophitee not required. nonpairment Asses safely and Not discused popriton of no 2 Lets. CD elow norm ART. stable regimen for 28 weeks and explore is completed plot or 2 2 SD below VL: not specified norton, neuron 10 weeks of norm on 1 test. norm on 1 test. norm on 1 test. norton, neuron not cophitie HAND: Any copritie inpairment Asses safely and Not discused not nor 2 SD below<	Single-arm,		ART: stable regimen for ≥ 12 weeks	dose oral Li on		absolute	Sex: 88% male	
but not required. but not required. performance of performed but with HV-associated and CSP preferred but with HV-associated not required. score (GDS ¹) v1 = -400 copresive in plasma people diagnosed isgnosed score (GDS ¹) r = 10 ¹⁴ and CSP preferred but inplasment with HV-associated implasment r = 10 ¹⁴ impairment: 21 Age: not specified implasment score (GDS ¹) r = 10 ¹⁴ impairment: 21 Age: not specified implasment score (GDS ¹) r = 10 ¹⁴ impairment: 21 Age: not specified implasment score (GDS ¹) r = 10 ¹⁴ impairment: 21 Age: not specified implasment score (GDS ¹) r = 10 ¹⁴ impairment: 21 Age: not specified implasment score (GDS ¹) r = 10 ¹⁶ impairment: 21 Age: not specified implasment score (GDS ¹) r = 10 ¹⁷⁶ impairment: 21 Age: not specified implasment score (GDS ¹) r = 11 ¹⁷⁶ impairment: 21 Age: not specified implasment score (GDS ¹) r = 11 ¹⁷⁶ impairment: 21 Age: not specified implasment score (GDS ¹) r = 11 ¹⁷⁶ impairment: Age: score or cognitive implasment score (GDS ¹) of Li r = 11 ¹⁷⁶ impairment: Age: score or cognitive implasment of Li of Li	open-label pilot		CD4 count: <500 cells/µL preferred	neuropsychological		global deficit	Age (mean): 44 years	
VL: -400 copie/mL in plasma people diagnosed and C5 preferred but not required. VL: -400 copie/mL in plasma and C5 preferred but not required. with HV-associated impairment with HV-associated impairment call ¹⁴ impairment: 21 Age: not specified and explore is impairment: 21 Age: not specified and explore is and explore	<i>n</i> = 8		but not required.	performance of		score (GDS ⁴)	Race/Ethnicity: 50/12.5% white/black	
and C5 preferred but with HV-associated not required. In the impairment inpairment tal) ¹⁴ in mairment: ≥1 Avery cognitive impairment Assess safety and Not discussed Proportion of 1 2 SD below norm ART: stable regiment for 28 weeks and explore its subjects who in on ≥2 tests, CD4 count: not specified and explore its completed norm on 1 test. CD4 count: not specified turner(on, and in the originally biomarkers. Assess safety and Not discussed proportion of 1 al) ¹⁶ impairment: ≥1 Age: not specified turner(on, and in the originally biomarkers. assess safety and Not discussed for assess safety and in the originally biomarkers. a safety and in the originally biomarkers. a safety and in the originally biomarkers. a safety and Not discussed for a subjects who assess safety and Not discussed for a subjects of the impairment: Ages: not specified to the ability of CPI. Arrively assess safety and Not discussed in the originally biomarkers. a safety and Not discussed in the originally biomarkers. Arrively for the originally biomarkers. Arrively for the and a subjects of the addition of the add			VL: <400 copies/mL in plasma	people diagnosed			Education (mean): 14 years	
Indicative Indicative impairment neurocognitive impairment tal.) ¹⁴ impairment: 21 Age: not specified Proportion of total impairment tal.) ¹⁴ impairment: 21 Age: not specified Not discussed Proportion of total impairment tal.) ¹⁴ impairment: 21 Age: not specified and explore is completed pilot on 22 tests, CD4 count: not specified traction, and traction, and norm on 1 test. Yu: not specified fifect on cognition, 10 weeks of total inpairment at neuroimaging cognitive Norm on 1 test. Yu: not specified traction, and traction, and cognitive Age: not specified turction, and turction, and turction, and cognitive Norm on 1 test. Age: not specified turction, and turction, and cognitive Age: not specified turction, and turction, and of ti. dot2 SD below Age: not specified turction, and turction, and of ti. dot2 SD below Age: not specified turction, and turction, and of ti. dot2 SD below Age: not specified turction, and turction, and of ti.			and CSF preferred but	with HIV-associated			Duration HIV+: not reported	
impairment impairment impairment impairment cognitive HAND: Any cognitive impairment Assess safety and Not discussed Proportion of La1 ¹⁴ impairment: 21 Age: not specified to a subjects who and explore its and explore its completed plot on 22 SD below norm ART: stable regimen for 28 weeks and explore its completed on 22 SD below VL: not specified truction, and turction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and norm on 1 test. CD4 count: not specified truction, and turction, and norm on 1 test. CD4 count: not specified truction, and turction, and norm on 1 test. CD4 count: not specified truction and turction and turction and norm on 1 test. CD4 count: not specified truction, and turction, and turction and norm on 1 test. CD4 count: not specified truction and turction and turction and norm on 1 test. Age: not specified truction and turction and turction and turction and norm on 1 test. Age: not specified truction and turction and turctin and turction and turction and turctin and tur			not required.	neurocognitive			CD4 count (mean): 292 cells/mm ³	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed Proportion of 1 t al) ¹⁴ impairment: ≥1 Age: not specified aller explained Not discussed Proportion of 1 c SD below norm ARI: stable regiment for ≥8 weeks and explore its completed subjects who c SD below norm ARI: stable regiment for ≥8 weeks and explore its completed plot on ≥2 tests, CD4 count: not specified tunction, and treatment at or ≥2 SD below VL: not specified tunction, and treatment at norm on 1 test. CO4 count: not specified tunction, and treatment at norm on 1 test. NL: not specified tunction, and treatment at norm on 1 test. Allo: Any cognitive impairment assigned dose assigned dose biomarkers. of ti. assigned dose biomarkers. to t discussed. Whether or assigned dose impairment. Ages: not specified to t discussed. of ti.				impairment			CD4 nadir: not reported	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed Proportion of 1 t al) ¹⁴ impairment: ≥1 Age: not specified total completed subjects who r S D below norm ART: stable regimen for ≥8 weeks and explore its completed pllot on ≥2 tests, C D4 count: not specified turction, and turction, and treatment at or ≥2 SD below VL: not specified function, and turction, and treatment at or ≥2 SD below VL: not specified function, and treatment at or ≥2 SD below VL: not specified function, and treatment at or ≥2 SD below VL: not specified function, and treatment at or ≥2 SD below VL: not specified function, and treatment at or ≥2 SD below VL: not specified function, and treatment at or ≥2 SD below VL: not specified function, and treatment at norm on 1 test. ARD: Any cognitive impairment Assess safety and Not discused. fils6 impairment: Ages: not specified tolenablity of CPi- not the add 21 SD below ARD: stable regimen for >8 weeks. 1180 in treating subjected							Plasma VL: 87.5% with ≤400 copies/mL	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed Proportion of 1 t al.) ⁴ impairment: 21 Age: not specified tolerability of Li subjects who . 5D below norm AR1: stable regimen for >8 weeks and explore its subjects who . 5D below norm AR1: stable regimen for >8 weeks and explore its completed . 0 n ≥2 tests, CD4 court: not specified function, and nore congniton, norm on 1 test. VL: not specified neuroimaging the originally norm on 1 test. Am2: Any cognitive impairment Assess safety and Not discussed. Whether or al. cognitive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or al. 21 SD below AR1: stable regiment for >8 weeks. 1183 in treating of Li.							Injection drug use: active psychoactive	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed Proportion of 1 t al.) ¹⁴ impairment: 21 Age: not specified tolerability of Li subjects who . 5D below norm ART: stable regimen for 28 weeks and explore its subjects who pilot n 22 tests, CD4 court: not specified incrition, and norm on 2 norm on 1 test. VL: not specified function, and neuroimaging the originally norm on 1 test. Age: not specified neuroimaging of Li. . Cognitive HAND: Any cognitive impairment Assess safety and Not discussed Not discussed . 13 ¹⁰⁶ inpairment: Ages: not specified tolerability of CP- of Li.							drug abuse excluded	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed Proportion of 1 t al.) ¹⁴ impairment: 21 Age: not specified tolerability of Li subjects who . 5 D below norm ART: stable regimen for 28 weeks and explore its completed plot n ≥ 2 tests, CD4 count: not specified tolerability of Li 10 weeks of norm on 1 test. CD4 count: not specified function, and neuroimaging the originally norm on 1 test. VL: not specified turction, and neuroimaging the originally norm on 1 test. Cognitive impairment Assess safety and Not discussed of Li. additive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or additive Additive impairment Assess safety and Not discussed. Not discussed. Not the additive Additive impairment Assess safety and Not discussed. Not the of Li.							Karnofsky Score: all ≥50	
et al.) ¹⁴ impairment: 21 Age: not specified tolerability of Li subjects who 1, SD below norm ART: stable regimen for 28 weeks and explore its completed 2 lepiot on 22 tests, CD4 count: not specified effect on cognition, and or 22 SD below VL: not specified to recimaging the originally norm on 1 test. The environment of the completed to the originally norm on 1 test. CD4 count: not specified to the completed to the originally norm on 1 test. CD4 count: not specified to the completed to the originally assigned dose to the completed to the completed to the originally the originally the originally the originally assigned dose to the completed to the completed to the original to the original to the completed to the complet	j.Lithium (Li)	Cognitive	HAND: Any cognitive impairment	Assess safety and	Not discussed	Proportion of	HAND: not reported	10 weeks
n, 5D below norm ART: stable regimen for ≥8 weeks and explore its completed el plot on ≥2 tests, CD4 count: not specified effect on cognition, 10 weeks of or ≥2 SD below VL: not specified function, and 10 weeks of 10 weeks of or ≥2 SD below VL: not specified function, and 10 weeks of 10 weeks of norm on 1 test. NL: not specified function, and treatment at norm on 1 test. 0 test. assigned dose filt norm on 1 test. of ti. filt Ages: not specified Assess safety and Not discussed. filt Ages: not specified to learability of CP- not the ed, ≥1 SD below ART: stable regimen for ≥8 weeks. 1189 in treating subjected	(Schifitto et al.) ¹⁴	impairment: ≥1	Age: not specified	tolerability of Li		subjects who	Sex: 67% male	
Is plot on ≥2 tests, CD4 count: not specified effect on cognition, and treatment at norm on 1 test. (D weeks of function, and function, and treatment at norm on 1 test. (D weeks of function, and function, and norm on 1 test.) (D weeks of function, and function, and function, and function, and assigned dose assigned dose of the normalized dose of the northe northe normalized dose dose of the northe normalized dose of the no	Single-arm,	SD below norm	ART: stable regimen for \geq 8 weeks	and explore its		completed	Age (mean \pm SD): 47.5 \pm 5.5 years	
or ≥2 SD below VL: not specified function, and treatment at norm on 1 test. NL: not specified the originally norm on 1 test. I assigned dose biomarkers. assigned dose of Li. of Li. of Li. of Li. of Li. of Li. determinent: Ages: not specified to to be abliny of CP- not the not the ced. ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected subjec	open-label pilot	on ≥2 tests,	CD4 count: not specified	effect on cognition,		10 weeks of	Race/Ethnicity: 60/40% white/black	
norm on 1 test. neuroimaging neuroimaging the originally the originally biomarkers. assigned dose assigned dose of Li. of Li. of Li. of Li. of Li. of Li. table impairment: Ages: not specified to tolerability of CPI- not the original to the tolerability of CPI- not the subjected subjected to the subjected to the training to the subjected to the subjected to the training to the training to the subjected to the training to the subjected to the training to the subjected to the training	<i>n</i> = 15	or ≥2 SD below	VL: not specified	function, and		treatment at	Education (mean \pm SD): 11.2 \pm 1.4 years	
biomarkers. biomarkers. assigned dose assigned dose assigned dose of Li. of Li. of Li. of Li. assess afery and Not discussed. Whether or Li impairment: Ages: not specified to tolerability of CPI- not the ced. ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected subjected		norm on 1 test.		neuroimaging		the originally	Duration HIV+ (mean \pm SD): 12.1 \pm 5.4	
of Li. Cognitive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or 1 impairment: Ages: not specified to tolerability of CPI- not the ced, ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected				biomarkers.		assigned dose	CD4 count (mean \pm SD): 329 \pm 207 cells/mm ³	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or 1 et al.) ³⁶ impairment: Ages: not specified to tolerability of CPI- not the ted, ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected						of Li.	CD4 nadir: not reported	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or I impairment: Ages: not specified to tolerability of CPI- not the ced, ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected							Plasma VL: 60% with <50 copies/mL	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or 1 impairment: Ages: not specified to tolerability of CPI- not the ced, ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected							Injection drug use: not reported	
Cognitive HAND: Any cognitive impairment Assess safety and Not discussed. Whether or 1 et al.) ³⁶ impairment: Ages: not specified tolerability of CPI- not the eed, ≥1 SD below ART: stable regimen for ≥8 weeks. 1189 in treating subjected							Karnofsky Score (mean): 87	
impaiment: Ages: not specified tolerability of CPI- not the ≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected	k.CPI-1189	Cognitive	HAND: Any cognitive impairment	Assess safety and	Not discussed.	Whether or	HAND: not reported	10 weeks
≥1 SD below ART: stable regimen for ≥8 weeks, 1189 in treating subjected	(Clifford et al.) ³⁶	impairment:	Ages: not specified	tolerability of CPI-		not the	Sex: 84% male	
	Ran domized,	≥1 SD below	ART: stable regimen for ≥8 weeks,	1189 in treating		subjected	Age (mean): 43.4 years	

(Continued)

udy e ATA, dL) ³²	norm on 22 tests, or 22 SD below norm on 1 test. dysfunction: 21.5 SD below norm 22.5 SD below mean 0.1 test. =21.5 SD below norm 0.2 tests, norm 0.1 test.	if on ART. CD4 count: not specified VL: not specified VL: not specified HAND: Any cognitive dysfunction. Estatified on severity of impairment (severe, mild-moderate) Ages: 18-60, stratified on range (18-39, 40-60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	HIV-associated cognitive-motor impairment		completed	Race/Ethnicity: 52% white	
ت ۲۹.۰۰۰ ۲۰	D below n 1 test. zioni ≥1.5 2w norm tests, or 0 below n 1 test. 2 below n 2 tests, n 1 zest. n 1 zest. n 1 zest.	CD4 count: not specified VL: not specified HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	cognitive-motor impairment			mental and a second of the second sec	
ت ۲	n 1 test. cion: ≥1.5 www.norm below n 1 test. ysfunction: D below	 VL: not specified HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18-60, stratified on range (18-39, 40-60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago) 	impairment		the study on	Education (mean): 14 years	
, A, C	tion: ≥1.5 www.norm below n 1 test. ysfunction: D below n 22 tests, n n 22 tests,	HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)			the original	Duration HIV+ (mean): 7.9 years	
A, A	tion: ≥1.5 www.norm below n 1 test. ysfunction: D below n 12 tests, n n ≥2 tests,	HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)			dose of	CD4 count (mean): 262 cells/mm ³	
A, C	tion: ≥1.5 www.norm lests, or below an 1 test. 2 below 2 below	HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)			medication.	CD4 nadir: not reportedLog10	
A, [.] ³⁷	tion:≥1.5 2w norm lests, or 5 below an 1 test. 2 below 2 below 1 rest. 2 below	HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)				Plasma VL (mean): 3.6 copies/mL	
A, [] ³⁷	tion: ≥1.5 www.norm lests, or > below m 1 test. 2 below D below m ≥2 tests,	HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)				Injection drug use: not reported	
A, C.	tion: ≥1.5 w norm sests, or 5 below an 1 test. D below D below	HAND: Any cognitive dysfunction. Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)				Karnofsky Score (mean): 83	
2	tion: ≥1.5 ww norm æsts, or below nn 1 test. Sefunction: D below on ≥2 tests,	Stratified on severity of impairment (severe, mild-moderate) Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	Determine whether	Dose and route	6-month	HAND: 66% severe deficit	6 months
al.) ³⁷	w norm :ests, or) below on 1 test. D below n ≥2 tests,	(severe, mild-moderate) Ages: 18-60, stratified on range (18-39, 40-60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	intranasal peptide	(intranasal)	change global	Sex: 95% male	
	ests, or 5 below nn 1 test. ysfunction: D below n ≥2 tests,	Ages: 18–60, stratified on range (18–39, 40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	T improves	based on	neuropsychological	Age: 57% 18–39 years	
) below n 1 test. ysfunction: D below n ≥2 tests,	40–60) ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	cognitive function	previous data	z-score	Race/Ethnicity: 82/5% white/black	
	ysfunction: 5 below on ≥2 tests,	ART: None within 4 weeks or any stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)	in HAND	from limited	summarizing	Education (mean): 15 years	
double-blind, mean o	ysfunction: D below on ≥2 tests,	stable standardized regimen for ≥12 weeks. Stratified on use (yes, no) and length of use (never, ≤3 months ago, >3 months ago)		PK and Phase I	23 measures	Duration HIV+ (mean): not reported	
placebo- Severe dy) below in ≥2 tests,	Stratified on use (yes, no) and length of use (never, \preceq months ago, >3 months ago)		studies		CD4 count (mean): 53% with \leq 00 cells/mm ³	
controlled study ≥1.5 SD	in ≥2 tests,	(never, ≤3 months ago, >3 months ago)				CD4 nadir: not reported	
<i>n</i> = 215 norm o	and delation					Plasma VL: not reported	
one of which was	Which was	CD4 count: not specified, stratified on count				Substance Abuse: 56% previous use	
≥2.5 SE	≥2.5 SD below	(<200, 200–500, >500 cells/mm ³)				Karnofsky Score: not reported	
шош		VL: not specified					
I1.D-Ala ₁ -peptide As above ²⁹	29	As above ²⁹	Examine if	As above ²⁹	6-month change	CSF VL Studies ⁵ :	6 months
T-amide (DAPTA,			intranasal		in CSF and	HAND: 58% severe deficit	
or Peptide T)			DAPTA is		peripheral VL	Sex: 98% male	
(Goodkin et al.) ³⁸			associated			Age (mean): 40 years	
Retrospective			with a			Race/Ethnicity: 85/4% white/black	
substudy of above			reduction in			Education (mean): 15.2 years	
randomized,			CSF and			Duration HIV+: not reported	
double-blind,			peripheral VL			CD4 count: 45% with \leq 200 cells/mm ³	
placebo-			among a			CD4 nadir: not reported	
controlled study ²⁷			subgroup of			Plasma VL: not reported	
n = 92 (for CSF			participants			Substance Abuse: 61% previous use	
studies), $n = 57$			enrolled in			Karnofsky Score: not reported	
(for peripheral			the study				
studies)			above ³⁷				
m.Lexipafant Cognitive	_	HAND: Any cognitive impairment.	Assess the safety	Not discussed	Whether or not	HAND: Global impression: 7/50/37/7%	10 weeks
(Schifitto et al.) ³⁹ impairment:	nent:	Ages: not specified	and tolerability,		the subjected	normal/mild/moderate/severe	
Randomized, ≥1 SD below	below	ART: stable regimen for ≥6 weeks	of lexipafant in		completed the	impairment	
double-blind, norm o	nom on≥2 tests,	CD4 count: not specified	HAND		study on the	Sex: 73% male	
placebo-controlled or ≥ 2 S	or ≥2 SD below	VL: not specified			original dose of	Age (mean): 42.6 years	
study norm o	nom on 1 test.				medication.	Race/Ethnicity: 43% white	
n = 30 Global im	Global impression					Education (mean): 13.4 years	

Table 1. Continued.

Table 1. Continued	.be						
		Target population (key inclusion and					
Trial and design	Case definitions	exclusion criteria)	Objective of trial	Dose selection	Primary outcome	Selected covariates and confounders	Study duration
	of cognitive					Duration HIV+ (mean): 6.5 years	
	function assessed					CD4 count (mean): 390 cells/mm ³	
	by neuro-					CD4 nadir: not reported	
	psychologist,					Plasma VL: not reported	
	does not exclude					Illicit drug use: none reported during trial	
	abnormal NP					Karnofsky Score (mean): 81	
	test scores						
n.OPC-14117	MSK staging	HAND: Any cognitive impairment	Assess the safety	Not discussed	Whether or not	HAND: 53/47% ADC 0.5/1	12 weeks
(The Dana	Cognitive	Ages: not specified	and tolerability		the subjected	Sex: 83% male	
Consortium 1997) ⁴⁰	impairment:	ART: stable regimen for ≥ 6 weeks	of OPC-14117		completed the	Age (mean): 41.7 years	
Randomized,	≥1 SD below norm	CD4 count: not specified			study on the	Race/Ethnicity: 57/37% white/black	
double-blind,	on ≥ 2 tests, or	VL: not specified			original dose	Education (mean): 13.5 years	
placebo-	≥2 SD below				of medication.	Duration HIV+ (mean): 5.3 years	
controlled study	norm on 1 test.					CD4 count (mean): 234 cells/mm ³	
n = 30						CD4 nadir: not reported	
						Plasma VL: not reported	
						Illicit drug use: none reported during trial	
						Karnofsky Score (mean): 85	
	minodaficiancy virus-a	accoriated neuroconnitive dicorder. N	MD mild partrocoduit	iva disordar: ART 3	intiratroviral therapy:	HAND human immundaficiana virus-secoristad nauroconnitiva dicordar. MND mild nauroconnitiva dicordar. ART stratrovical thereaver VI. viral load: MCK. Mamorial Sloan Kattarina	ttaring
^a Uganda Neuropsv	riuriouericiericy virus-c ch Test Battery Sumn	associated riediocognitive disorder, iv mary Measure: Grooved Pegboard do	multime treat occupiting the second	nant hand, Color T	iriureu ovirar urerapy, rails 1 & 2, Symbol [userial minimuodencienty mosessociated neurocognitive disorder, Miruz, mini neurocognitive disorder, Ant, antineurovial menapy, v.r. vira load, Merubala sidan retennig. Uganda Neuropsych Test Battery Summary Measure: Grooved Pedboard dominant and nondominant hand, Color Trails 1 & 2, Symbol Digit Test, WHO-UCLA Verbal Learning test trial 5 total.	test trial 5 total,
WHO-UCLA Verba	l Learning Test delaye	WHO-UCLA Verbal Learning Test delayed recall, Digit Spans forwards and backwards.	ackwards.				
^b NPZ8: Trail Makin	NPZ8: Trail Making Test parts A and B, Grooved Pegboard		ant and nondominant	hand, CalCAP Cho	ice and Sequential Re	Test with dominant and nondominant hand, CalCAP Choice and Sequential Reaction Test Time, Timed Gait Test, Symbol Digit Test.	Ibol Digit Test.
"NPZ6: Rey Audito	^c NPZ6: Rey Auditory Verbal Learning (total number correct		all), Grooved Pegboai	rd Test with domin	ant and non-domina	and delayed recall), Grooved Pegboard Test with dominant and non-dominant hand, CalCAP Choice and Sequential Reaction Time	ial Reaction Time
Test.							
^d GDS (Global Defic	cit Score): A mean det	ficit score derived from multiple indiv	vidual test deficit score	is (based on T score	es) of the following m	^d GDS (Global Deficit Score): A mean deficit score derived from multiple individual test deficit scores (based on T scores) of the following measures: Hopkins Verbal Learning Test-Revised, Brief Vi-	-Revised, Brief Vi-

suospatial Memory Test-Revised, Controlled Oral Word Association Test, semantic verbal fluency, Stroop color-Word Test, Train Making Test, Parts A and B, Wisconsin Card Sorting Test-64 Card Version, Halstead Category Test, Paced Auditory Serial Addition Test, Grooved Pegboard Test, the Digit Symboy, Symbol Search, and letter-Number Sequencing tests from the Wechsler Adult Intelligence Scale-Third Edition^{41.}

^{ep}eripheral VL Studies had a slightly different covariate mix, but are not presented here for the sake of brevity.

Case ascertainment	Cannot define a target population or an outcome measure without a clear framework for defining the various subtypes of HAND.
Target population and goals of therapy	Inclusion/exclusion criteria must be determined independently for each candidate drug based on the proposed case definitions, mechanism of action, and goal of therapy. There is a high risk of a falsely negative trial if attention is not paid to focusing the primary question of efficacy on a specific population
Dose selection	Dose selection must be based on preclinical data and PK/PD in HIV-infected subjects and samples. If it is not, investigators cannot know if the appropriate concentrations of therapies are being achieved for the proposed mechanism of action
Primary outcome	Primary outcome measures of clinical efficacy should be standardized across trials. Readers must be careful not to use a trial powered to assess safety and tolerability to determine clinical efficacy in HAND. Outcome measures examining secondary endpoints such as changes in neuroimaging may be useful in select circumstances based on the proposed mechanism of action of a candidate therapy
Confounders and interactions	Covariates that act as confounders or interactions in the proposed mechanism of action of a candidate drug must be accounted for to avoid masking a true treatment effect. Thought should be given in particular to covariates that have a known biological effect on HAND or HIV immunology (including, but not limited to, gender, age, CD4 nadir, etc.)
Study duration	Study durations must be defined based on the primary question of a trial. Durations of less than a year may not be long enough to see a true effect on cognitive function. In addition, results of too frequent neuropsychological testing may confound results by introducing a practice effect

Table 2. Targetable components of trial design to maximize likelihood of seeing an effect in adjuvant therapy trials for HAND.

HAND, human immunodeficiency virus-associated neurocognitive disorder.

classification of HAND because the gradations of functional impairment it quantifies include deficits due to both neurocognitive deficits and myelopathy. In 2001, the AIDS task force of the American Academy of Neurology (AAN) proposed the first diagnostic set of criteria specific to HAND,¹⁸ including the two broad categories of HAD and minor cognitive-motor disorder (MCMD), to represent a milder version of cognitive impairment compared to frank dementia. When cART became available in 1996, the prevalence of HAD in HIV-infected adults shifted from estimates of 10–15% to closer to 2%¹, while milder disorders became more common. Thereafter, in 2007, Antinori et al. proposed the current Frascati diagnostic definitions of HAD, MND, and ANI to better distinguish the milder forms of HAND.¹⁹ Table 3 describes each of these diagnostic criteria in detail.

Current literature examining neurocognitive data in HIV uses a variety of these definitions to describe cognitive impairment in target populations and to assess interventions. Some of this variation is related to when the trial was performed and the working definitions of that time, but not all. Three studies in this group of trials define HAND using MSK staging (b, d, d1), one uses AAN criteria (i), and one uses Frascati criteria (a). However, most trials incorporate unvalidated definitions of cognitive impairment (n = 13) that vary across studies. Specifically, one trial (c) defines cognitive impairment as ≥ 1 SD below norm on ≥ 3 tests, or ≥ 2 SD below norm on 1 test $+ \ge 1$ SD below norm on a 2nd test, where as other trials (e-h, j, k, m, n) use the definition of ≥ 1 SD below norm on ≥ 2 tests, or ≥ 2 SD below norm on 1 test. Finally, some trials (l, l1) use the definition of \geq 1.5 SD below norm on \geq 2 tests, or \geq 2.5 SD below mean on 1 test. While

each different set of case definitions is internally consistent within a trial and appropriate to the era when the trial was performed, readers must attend closely to case ascertainment when reviewing a trial to ensure they understand how to later generalize results, because MCMD is not directly equivalent to MND, nor is MSK stage 0.5 equivalent to ANI. As all clinical case criteria in medicine evolve with new understanding of disease pathophysiology, if the current HAND classification criteria do not serve the needs of clinical trialists, then the larger HAND research community should revise the classification again to one more functionally suited to the clinical issues.

Target population and goal of therapy

Once case definitions for HAND are established, a target population for adjuvant therapy investigation must be clearly identified. Prior to the cART era, HAD was an easy clinical target. HAD was prevalent in HIV infection, related to significant morbidity and mortality, and effectively treated with antiretroviral therapy. In recent years, as HAND has shifted to milder manifestations such as MND and ANI,¹⁹ target populations have become more complex.

The natural course of temporal progression among the different subcategories of HAND in the cART era is not well understood.^{9,20} Over time, individuals with ANI have an increased risk of progression to more severe forms of HAND,^{9,21–23} and both ANI and MND predict HAD-associated neuropathological changes.^{9,24} Progression across MSK and AAN stages is less well defined, which makes these classification schemes more problematic to study. While the Frascati subcategories may be on a

Table 3.	Diagnostic	classification	of	HIV-associated	neurocognitive	disorders over time	

Frascati Cr	iteria (2007) ¹⁹
ANI	Asymptomatic neurocognitive impairment Neuropsychological performance at least 1 SD below demographically matched normative scores in at least 2 cognitive domains ¹ .
	Cognitive impairment does not interfere with everyday functioning
MND	Mild neurocognitive disorder Neuropsychological performance at least 1 SD below demographically matched normative scores in at least 2 cognitive domains ¹ .
	Cognitive impairment results in mild interference in daily functioning
HAD	HIV-associated dementia Neuropsychological performance at least 2 SD below demographically matched normative scores in at least 2 cognitive domains ¹ .
	Cognitive impairment results in marked interference in daily functioning
	Academy of Neurology (AAN) Criteria (2001) ¹⁸
MCMD	Minor cognitive-motor disorder Acquired abnormality in at least two of the following cognitive/motor/behavioral domains for >1 month verified by clinical neurologic examination or neuropsychological testing: impaired attention/concentration, mental slowing, impairment memory, slowed movements, impaired coordination, or personality change/irritability/emotional liability ¹ .
	Disturbance from cognitive/motor/behavioral abnormalities causes mild impairment of work or activities of daily living
HAD	HIV-associated dementia Acquired abnormality in at least two of the following <i>cognitive</i> domains for >1 month causing impairment in work or activities of daily living: attention/concentration, speed of information processing, abstraction/reasoning, visuospatial skills, memory/learning, speech/language ¹ .
	At least one of the following: (1) acquired abnormality in motor function or (2) decline in motivation, emotional control, or social behavior.
Memorial :	Sloan Kettering (MSK) Staging (1988) ¹⁷
ADC 0.5	Equivocal/subclinical cognitive impairment Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform ADLs. Gait and strength are normal
ADC 1	Mild dementia Able to perform all but the more demanding aspects of work or ADL but with unequivocal evidence of functional intellectual or motor impairment. Can walk without assistance
ADC 2	Moderate dementia Able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. Ambulatory, but may require a single prop.
ADC 3	Severe dementia Major intellectual incapacity (cannot follow news or personal events, sustain complex conversation, etc.) or motor disability (cannot walk unassisted, usually with slowing, and clumsiness of arms as well).
ADC 4	End stage dementia Nearly vegetative. Intellectual and social comprehension and output are rudimentary. Nearly or absolutely mute. Paraparetic or paraplegic with urinary and fecal incontinence.
1	paraplegic with urinary and fecal incontinence.

¹Impairments must not be explained by comorbid conditions (such as central nervous system [CNS] opportunistic infections, drug or alcohol abuse, or prior brain injury), and individual may not meet criteria for delirium or dementia.

spectrum of the same pathogenesis, this question also remains somewhat unclear. Finally, even if these subcategories are related, an individual with HAD and a 20-year duration of infection may respond differently to a given adjuvant therapy than an individual with ANI and a 2-year duration of infection.

An ideal target population for adjuvant therapy must be determined independently for each candidate drug based on the proposed case definitions, mechanism of action, and goals of therapy. For example, the goal of one therapy may be to improve cognitive testing and subjective functioning in an individual with HAD. Alternatively, in an individual with ANI without clear functional impairment, the goal may be to prevent this progression over time, and improvement in cognitive evaluation from a minimally abnormal baseline may be irrelevant.

Past investigations have considered a variety of different target populations. Specifically, some trials targeted subjects with any cognitive impairment (e, e1, e2, f, g, j, k, l, l1, m, n), some targeted only those with more severe types of impairment (a, d, d1, i), one targeted those with milder impairment (b), others specifically target those with progressive decline (c), and one did not require cognitive impairment for enrollment (h). However, the rationale behind these choices has not been based on a clear mechanistic process that is obvious to the reader. In addition, inclusion/exclusion criteria vary widely between trials. Some choose populations based on age (b, c, f, g, i, l, l1), various cART restrictions (b, c, d, d1, e, e1, e2, f, g, i, j, l, l1, m, n), CD4 count (b, i), and viral load (VL) (a), but not all specify these parameters. We feel that broadly treating all subjects with any measure of cognitive impairment without defined age/cART/CD4/VL data is not a useful approach, as it may obscure treatment effect in a smaller subgroup of individuals depending on the outcome of interest and result in an inappropriately negative trial. While the actual number of subjects available for enrollment needs to be balanced with these trial design ideals, there is a high risk of a false-negative trial if attention is not paid to the primary question of efficacy in a specific population.

Once a target population is identified in study inclusion/exclusion criteria and subjects are recruited, a description of what type of HAND is enrolled in a trial is essential for appropriate study interpretation. For example, one study in Table 1 (a) aimed to include subjects with both MND and HAD,²⁵ but was only successful in recruiting subjects with MND. Another study (i) aimed to include subjects with both MCMD and HAD, but did not report these baseline characteristics in their enrolled population.

Dose selection

The pharmacokinetics (PK) and pharmacodynamics (PD) of a candidate adjuvant drug may be altered as a consequence of the underlying pathophysiology of HIV, and may differ from data reported for other indications. Therefore, Phase I and II trials should be conducted in HIV+ patients with dose selection incorporating the underlying pathophysiology, not simply bridged from other indications. It is essential to study PK/PD and drug–drug interactions (DDIs) with cART regimens and other common co-medications to ensure proper dose selection for the target population. The frequent polypharmacy in this population can elicit untoward effects on clinical outcomes and can contribute to postmarketing failures of candidate adjuvant drugs when not thoroughly evaluated in the context of patient trials. Studies (I) and (11) were the only trials in this group that clearly defined a preclinical rationale for dose selection in their manuscripts. Others used doses for other indications (a) or based on *in vitro* or mechanistic data (f, g). The majority of trials do not comment on the rationale for dose selection (b–e2, h–k, m–n). While these trials may have had very clear rationale for their choices and omitted this data for brevity, this omission makes an understanding of the dose selected difficult to assess when later evaluating the success or failure of the therapy.

Measurable outcomes

There are several basic outcome measures used routinely in the assessment of HAND today, including formal neuropsychological testing scores, as well as subjective and objective functional measures. Traditionally, composite Z-scores are assessed for various batteries of neuropsychological tests using age- and sex-adjusted normative values, with higher scores reflecting better performance. The composition of neuropsychological testing used, however, varies from study to study (see Footnotes 1-4, Table 1). Most trials reviewed here use various combinations of traditional neuropsychological testing subtests (b, c, d, e, e2, i, l), and one trial used an Alzheimer disease-specific assessment scale (a). This varied practice is problematic because it remains unclear if each battery yields a similar result, as they have not been directly compared to each other in HAND. In addition, variability in outcome measures makes generalizability and comparison among studies significantly more difficult. Finally, many early studies of adjuvant therapies for HAND were powered to assess only safety/tolerability (f, g, h, j, k, m, n), rather than efficacy of that therapeutic in HAND. Caution must be used in making decisions regarding therapeutic efficacy based on trials that are not appropriately powered.

Confounders and interactions

After consensus definitions of HAND are agreed upon, a population within HAND to treat is identified, and primary outcome measures are defined, confounding and interacting elements must be further examined to gain a better understanding of the actual biological effect of the proposed adjuvant therapy. Attention to these details will also impact reproducibility of results in larger trials. For example, a certain drug may have a different treatment effect on men with low nadir CD4 counts with ANI versus women with MND and high cerebrospinal fluid (CSF) VLs. If CD4 count and VL are not assessed in the population and controlled for, subtle treatment effects may be missed. We propose that specific covariates to examine closely in all candidate drug therapies of HAND at baseline should minimally include sex and race/ethnicity (to account for known differential immune function), patient age (older patients may have HIV-unrelated neuropathological changes consistent with Alzheimer's disease or other unrelated cognitive impairment), nadir CD4 count (multiple clinical studies suggest that a lower nadir CD4 count confers increased risk of HAND), coinfections (which may cause CNS damage and neurocognitive deficits independent of HAND), VL, and substance use (which may result in drug-induced neuronal injury and/ or excitotoxicity, altered viral replication, and disruption of the blood–brain barrier).

Study duration

Study duration has historically been short in the evaluation of adjuvant therapies for HAND; only one study assessed in this review was longer than 6 months. A short study duration may or may not be appropriate depending upon the goal of therapy, but is frequently a default due to constraints of cost and time. For example, if the goal of therapy is to prevent functional progression in subjects with ANI, subjects likely need to be followed up for longer than the median time to progression (~45 months).²¹ If the goal of the study is to assess safety, a shorter duration may be appropriate. Finally, if the goal of therapy is to assess a biological endpoint such as MR spectroscopy or markers of CNS inflammation, the duration of the trial needs to be tailored appropriately. Shortening the study duration needed to answer the specific question of the trial undermines the validity of the results, may mask true treatment effects, and may confound results by introducing a practice effect on test scores.

Designing an Optimal Trial for HAND

Thus far, we have reviewed previous trials in an attempt to identify study design elements that require more careful consideration as we move forward with new trials of adjuvant therapies for HAND. We hope to engage the HAND research community to bring the discussion to some measure of consensus based on the current neurobiological understanding of this disease.

On a practical level, many of these study design elements that we aim to optimize are difficult to control in the real world with the current funding climate. For example, patient recruitment has been notoriously difficult in HAND therapy trials, sometimes requiring several years to enroll only a handful of subjects. The reasons for this difficulty with patient accrual are complex, but likely related to multiple factors, including complex social situations, access to medical care, the time required to perform a careful neurocognitive assessment, aversion to study procedures such as lumbar puncture, or the general lack of concern in the HIV community at large regarding the long-term effects of HAND. In addition, given the prolonged mean time to progression in HAND, securing funding to conduct an appropriate longitudinal clinical study of a drug with unclear preclinical potential has been difficult.

Moving forward, based on both the design and practical problems described above, we advocate the concept of a two-step trial process, consisting of both "learning" and "confirming" trials²⁶ for candidate adjuvant therapies in HAND. This paradigm, originally proposed by Sheiner in the mid-1990s,²⁶ recognizes the historical emphasis of commercial drug development on confirmation, as it immediately precedes and justifies regulatory approval. However, the conditions of such Phase III (confirmatory) trials necessitate a great cost to the study sponsor as well as a potential risk. Therefore, in order to optimize success of confirmatory trials, learning must come first in order to address "an essentially infinite set of quantitative questions concerning the functional relationship between prognostic variables, dosage, and outcome."²⁶

The "Learning" trial

The purpose of a "learning" trial is to identify optimal target populations, dose ranges, mechanistic biomarkers of drug action and if possible, to establish correlation with relevant clinical outcomes. In HAND, we could consider enrolling subjects with HAD, MND, and ANI defined by Frascati criteria, aged 25-50 years into an adaptively designed "learning" trial. Constricting the age of enrollment eliminates adolescents with still developing neurologic and immune systems who may respond to therapy differentially, and the elderly who may have other primary sources of cognitive impairment; removing these populations would reduce the variability in response. Older and younger populations could later be studied separately as they likely manifest different disease trajectories. An adaptive trial design would permit enrichment of the responder population as well as more efficient randomization of patients to dose groups based on interim assessments of efficacy and futility status against a priori boundaries. With safety and activity milestones in place, patients could be randomized to one of three active dose groups or placebo at study initiation. Based on preclinical investigations of HIV-specific indications, doses would be assessed for both dose response and an absolute response compared to placebo. If one dose appeared more appropriate (based on protocol-specified metrics for both safety and activity), this study design would shift enrollment. In this learning stage, in order to keep results as generalizable as possible, restrictions would not be placed on most covariates (e.g., subjects with all CD4 counts and all

substance abuse would be included). Then, if there was suggestion of a positive effect but the study was underpowered due to a limited study population to adequately assess this based on the multitude of covariate subgroups, a population-based PK/PD model could be created to explore the boundaries of dose and response over time. Simulations based on such a model incorporating the overall adaptive design construct could define optimal accrual rates, decision rules/cutoffs, effect sizes, nominal alpha levels (if relevant), and minimal sample sizes. Multiple outcome measures would be evaluated, including neuropsychological scores, functional outcomes, and possibly advanced neuroimaging effects, such as changes in MRS. To optimally see a signal of effect, such a trial should likely last for a minimum of 2 years based on the natural history of HAND.

The "Confirming" trial

Hypotheses generated during the learning trial of adjuvant HAND therapy would subsequently be tested in a larger, more rigorous confirmatory trial. In general, confirmatory trials test if there is an effect of a given drug on the defined primary outcome. They usually include randomization to one of two treatment groups of equal size and target a homogenous group of subjects defined by more specific inclusion and exclusion criteria than applied in a learning trial. For example, a confirmatory trial of adjuvant therapy in HAND might focus on one subgroup of cognitive impairment (i.e., ANI) and include subjects with more restrictive baseline characteristics, such as specified CD4 cell counts or nadirs, plasma or CSF VL cutoffs, age, or specific cART regimens. In contrast to a learning trial, outcomes in confirmatory trials are usually limited to one or two clinical efficacy measures, such as lack of progression or cognitive improvement. There are still opportunities to learn in a confirmatory trial of adjuvant HAND therapy. For instance, in addition to change from baseline in neuropsychological test scores as the primary endpoint, subject covariates, drug exposure data, and additional clinical endpoints (e.g., changes in selected biomarkers and/or neuroimaging) can be collected and analyzed with a summary of such indices being part of the eventual drug monograph assuming the trial is positive. The inclusion of unique subgroups can also add variation without compromising the primary endpoint. Duration of the trial would depend on the specific questions being asked.

Moving Forward

In summary, there is an urgent need to better identify and treat patients with HAND in the cART era. To do

so though, the HAND research community needs to agree upon common investigative trial design elements to ensure that candidate therapeutics are adequately assessed in target populations before they are globally deemed unsuccessful. Even if the ideal adjuvant therapy is identified based on mechanism, and shown to cross the blood-brain barrier, has low protein binding, low DDI potential, a convenient dosing schedule, a broad therapeutic window, and manageable side effects, we will not be able to support its clinical benefit if we cannot demonstrate its efficacy. Once trial design elements are defined, a learning and confirming trial paradigm can be applied to more fully assess candidate therapies, incorporating adaptive Phase I/II study designs, modeling of the relevant dose-exposure-response targets, and projecting the appropriate population/goal of treatment-specific Phase III confirmatory studies. The proposed structure provides a framework from which other possibilities can be discussed. In general, this rational approach to the clinical evaluation of drug candidates is generalizable to other treatment trials in incompletely understood neurologic diseases.

Acknowledgments

The authors thank Carol Vincent Ph.D. and Dennis Kolson M.D., Ph.D. for their helpful review and comments of this manuscript. McGuire's training and research are supported by the National Institutes of Health (K12-NS049453). Barrett's research is supported by the National Institutes of (U01-MH090325, U54-HD071598, HHSN275 Health 201000003I, R01-FD004095-01A1). Spitsin's research is supported by the National Institutes of Health (U01-MH090325, R01-MH049981, R21-AI108298 [to S.D.D.]). Douglas's research is supported by the National Institutes of Health (R01-MH049981, 1U01-MH090325, UM1-AI69467, R21-AI108298, UO1HD040481). The content is the sole responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The work took place at The Children's Hospital of Philadelphia and The Children's Hospital of Philadelphia Research Institute. The authors had no conflicts of interest.

Author Contributions

All authors contributed in preparing, reviewing, and editing this manuscript.

Conflict of Interest

None declared.

References

- Heaton RK, Clifford DB, Franklin DR, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010;75:2087–2096.
- 2. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS 2011;25:1747–1751.
- 3. Valcour V, Paul R, Chiao S, et al. Screening for cognitive impairment in human immunodeficiency virus. Clin Infect Dis 2011;53:836–842.
- Ellis RJ, Deutsch R, Heaton RK, et al. Neurocognitive impairment is an independent risk factor for death in HIV infection. San Diego HIV Neurobehavioral Research Center Group. Arch Neurol 1997;54:416–424.
- 5. Ickovics JR, Hamburger ME, Vlahov D, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. JAMA 2001;285:1466– 1474.
- Sacktor N, McDermott MP, Marder K, et al. HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol 2002;8:136–142.
- Robertson KR, Robertson WT, Ford S, et al. Highly active antiretroviral therapy improves neurocognitive functioning. J Acquir Immune Defic Syndr 2004;36:562–566.
- Marra CM, Lockhart D, Zunt JR, et al. Changes in CSF and plasma HIV-1 RNA and cognition after starting potent antiretroviral therapy. Neurology 2003;60:1388– 1390.
- McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann Neurol 2010;67:699–714.
- González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. Nat Rev Immunol 2005;5:69– 81.
- Lindl KA, Marks DR, Kolson DL, Jordan-Sciutto KL. HIV-associated neurocognitive disorder: pathogenesis and therapeutic opportunities. J Neuroimmune Pharmacol 2010;5:294–309.
- Schifitto G, Navia BA, Yiannoutsos CT, et al. Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. AIDS 2007;21:1877–1886.
- Schifitto G, Peterson DR, Zhong J, et al. Valproic acid adjunctive therapy for HIV-associated cognitive impairment: a first report. Neurology 2006;66:919–921.
- Schifitto G, Zhong J, Gill D, et al. Lithium therapy for HIV-1 associated cognitive impairment. J Neurovirol 2009;15:176–186.
- Uthman OA, Abdulmalik JO. Adjunctive therapies for AIDS dementia complex. Cochrane Database Syst Rev 2008 Jul 16;(3)CD006496.

- 16. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clin Infect Dis 2013;56:1004–1017.
- Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988;158:1079–1083.
- Janssen RS, Cornblath DR, Epstein LG. 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;41:778–785.
- Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007;69:1789–1799.
- Tan IL, McArthur JC. HIV-associated neurological disorders: a guide to pharmacotherapy. CNS Drugs 2012;26:123–134.
- 21. Heaton R, Franklin D, Woods S, et al. Asymptomatic HIV-associated neurocognitive disorder (ANI) increases risk for future symptomatic decline: a CHARTER longitudinal study. Abstract #77. 19th Conference on Retroviruses and Opportunistic Infections (CROI); 5–8 March 2012; Seattle, WA: 2012.
- 22. McArthur JC, Brew BJ. HIV-associated neurocognitive disorders: is there a hidden epidemic? AIDS 2010;24:1367–1370.
- 23. Ellis R, Langford D, Masliah E. HIV and antiretroviral therapy in the brain: neuronal injury and repair. Nat Rev Neurosci 2007;8:33–44.
- Cherner M, Masliah E, Ellis RJ, et al. Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. Neurology 2002;59:1563–1567.
- Simioni S, Cavassini M, Annoni J-M, et al. Rivastigmine for HIV-associated neurocognitive disorders. A randomized crossover pilot study. Neurology 2013;80:553–560.
- 26. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997;61:275–291.
- 27. Nakasujja N, Miyahara S, Evans S, et al. Randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. Neurology 2013;80:196–202.
- 28. Sacktor N, Miyahara S, Deng L, et al. Minocycline treatment for HIV-associated cognitive impairment: results from a randomized trial. Neurology 2011;77:1135–1142.
- 29. Zhao Y, Navia BA, Marra CM, et al. Memantine for AIDS demential complex: open-label report of ACTG 301. HIV Clin Trials 2010;11:59–67.
- Schifitto G, Zhang J, Evans SR, et al. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. Neurology 2007;69:1314–1321.
- Schifitto G, Yiannoutsos CT, Ernst T, et al. Selegiline and oxidative stress in HIV-associated cognitive impairment. Neurology 2009;73:1975–1981.
- 32. Evans SR, Yeh T-M, Sacktor N, et al. Selegiline transdermal system (STS) for HIV-associated cognitive

impairment: open-label report of ACTG 5090. HIV Clin Trials 2007;8:437–446.

- Sacktor N, Schifitto G, McDermott MP, et al. Transdermal selegiline in HIV-associated cognitive impairment: pilot, placebo-controlled study. Neurology 2000;54:233–235.
- 34. A randomized, double-blind, placebo-controlled trial of deprenyl and thioctic acid in human immunodeficiency virus-associated cognitive impairment. Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders. Neurology 1998;50:645–651.
- Letendre SL, Woods SP, Ellis RJ, et al. Lithium improves HIV-associated neurocognitive impairment. AIDS 2006;20:1885–1888.
- Clifford DB, McArthur JC, Schifitto G, et al. A randomized clinical trial of CPI-1189 for HIV-associated cognitive-motor impairment. Neurology 2002;59:1568– 1573.
- 37. Heseltine PN, Goodkin K, Atkinson JH. Randomized double-blind placebo-controlled trial of peptide T for

HIV-associated cognitive impairment. Arch Neurol 1998;55:41-51.

- 38. Goodkin K, Vitiello B, Lyman WD, et al. Cerebrospinal and peripheral human immunodeficiency virus type 1 load in a multisite, randomized, double-blind, placebo-controlled trial of D-Ala1-peptide T-amide for HIV-1-associated cognitive-motor impairment. J Neurovirol 2006;12:178–189.
- Schifitto G, Sacktor N, Marder K, et al. Randomized trial of the platelet-activating factor antagonist lexipafant in HIV-associated cognitive impairment. Neurological AIDS Research Consortium. Neurology 1999;53:391–396.
- 40. Safety and tolerability of the antioxidant OPC-14117 in HIV-associated cognitive impairment. The Dana Consortium on the Therapy of HIV Dementia and Related Disorders. Am Acad Neurol 1997;49:142–146.
- 41. Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol 2004;26:307–319.