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REVIEW ARTICLE

Adjuvant therapies for HIV-associated neurocognitive disorders

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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.

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 disability[2] exposing affected individuals to financial errors and unsafe situations[3], and predicts non-CNS (central

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 incidence[6] 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 HAD[1]. 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 excitotoxicity[9–11]. 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 function[15], so no adjuvant therapies are recommended for routine clinical use[16]. 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 open-label 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

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

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

(*Continued*)

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
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 Karnofsky 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 NPZ8[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 Karnofsky Score (median [IQR]): 80 (70, 90)	Up to 60 weeks open-label extension.
e.Selegiline Transdermal System (STS) (Schifitto et al.)[30] Randomized placebo-controlled study (ACTG 5090) *n* = 128	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 safety, tolerability, and efficacy of STS for the treatment of HAND.	Not discussed	24-week change in absolute NPZ6[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)): 9.3 (5.5, 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) (Schifitto 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

(*Continued*)

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] Open-label treatment phase of above randomized placebo-controlled study[30] (ACTG 5090) *n* = 86	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)	Provide long-term safety (primary aim) and efficacy (secondary aim) of STS for the treatment of HAND.	Not discussed	24-week change (open-label period only) in absolute NPZ6[3].	HAND: not reported Sex: 86% male Age (median [IQR]): 46 (42, 52) years Race/Ethnicity: 51/33% white/black Education (median): not reported Duration HIV+: not reported CD4 count (median): 414 cells/mm^3 CD4 nadir: not reported Plasma VL: 36% with <50 copies/mL Injection drug use: not reported Karnofsky Score: 80% with ≥80	24 week open-label extension
f.Selegiline (STS) (Sacktor et al.)[33] Randomized, double-blind, placebo-controlled pilot study *n* = 14	MSK staging Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test	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 HAND.	Based on in vitro study of oral selegiline demonstrating synthesis of neuronal antiapoptotic genes in injured neurons.	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 Duration HIV+ (mean): 5.7 years CD4 count (mean): 294 cells/mm^3 CD4 nadir: not reported Plasma VL: not reported Injection drug use: not reported Karnofsky Score (mean): 81	10 weeks
g.Deprenyl (Selegiline) and thioctic acid (The Dana Consortium 1998)[34] Randomized, double-blind, placebo-controlled, 2 × 2 factorial design *n* = 36	MSK staging Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test.	HAND: Any cognitive impairment. Ages: ≥18 years ART: stable regimen for ≥6 weeks CD4 count: not specified VL: not specified	Assess safety, tolerability, and impact of deprenyl and thioctic acid on HAND	Deprenyl dose chosen to incompletely inhibit monoamine oxidase type B. Thioctic acid dose selection not discussed.	Whether or not the subjected completed the study on the original dose of medication.	HAND: 8/61/25/6% ADC 0/0.5/1/2–3 Sex: 72% male Age (mean): 41.2 years 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	10 weeks

(*Continued*)

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
h.Valproic acid (VPA) (Schifitto et al.)[13] Randomized, double-blind, placebo-controlled pilot study $n = 22$	Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test.	HAND: not specified. Stratified on impairment (unimpaired vs.impaired) Ages: not specified ART: not specified CD4 count: not specified VL: not specified	Assess safety and tolerability of VPA and explore its effect on cognitive performance and brain metabolism	Not discussed	10-week difference in tolerability between VPA and placebo.	HAND: 73/27% impaired/unimpaired Sex: 77% male Age (mean): 43.5 years Race/Ethnicity: 45/55% white/black Education (mean): 12 years Duration HIV+ (mean): 9.4 years CD4 count (mean): 434 cells/mm^3 CD4 nadir: not reported Plasma VL: 45% with <50 copies/mL Injection drug use: not reported Karnofsky Score (mean): 90	10 weeks
i.Lithium (Li) (Letendre et al.)[35] Single-arm, open-label pilot $n = 8$	AAN criteria	HAND: MCMD or HAD Age: 18–65 years ART: stable regimen for ≥12 weeks CD4 count: <500 cells/μL preferred but not required. VL: <400 copies/mL in plasma and CSF preferred but not required.	Determine the effects of low-dose oral Li on neuropsychological performance of people diagnosed with HIV-associated neurocognitive impairment	Not discussed	12-week difference in absolute global deficit score (GDS[4])	HAND: AAN categories not reported. Mean GDS = 0.74 Sex: 88% male Age (mean): 44 years Race/Ethnicity: 50/12.5% white/black Education (mean): 14 years Duration HIV+: not reported CD4 count (mean): 292 cells/mm^3 CD4 nadir: not reported Plasma VL: 87.5% with ≤400 copies/mL Injection drug use: active psychoactive drug abuse excluded Karnofsky Score: all ≥50	12 weeks
j.Lithium (Li) (Schifitto et al.)[14] Single-arm, open-label pilot $n = 15$	Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test.	HAND: Any cognitive impairment Age: not specified ART: stable regimen for ≥8 weeks CD4 count: not specified VL: not specified	Assess safety and tolerability of Li and explore its effect on cognition, function, and neuroimaging biomarkers.	Not discussed	Proportion of subjects who completed 10 weeks of treatment at the originally assigned dose of Li.	HAND: not reported Sex: 67% male Age (mean ± SD): 47.5 ± 5.5 years Race/Ethnicity: 60/40% white/black Education (mean ± SD): 11.2 ± 1.4 years Duration HIV+ (mean ± SD): 12.1 ± 5.4 CD4 count (mean ± SD): 329 ± 207 cells/mm^3 CD4 nadir: not reported Plasma VL: 60% with <50 copies/mL Injection drug use: not reported Karnofsky Score (mean): 87	10 weeks
k.CPI-1189 (Clifford et al.)[36] Randomized,	Cognitive impairment: ≥1 SD below	HAND: Any cognitive impairment Ages: not specified ART: stable regimen for ≥8 weeks,	Assess safety and tolerability of CPI-1189 in treating	Not discussed.	Whether or not the subjected	HAND: not reported Sex: 84% male Age (mean): 43.4 years	10 weeks

(*Continued*)

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
double-blind, placebo-controlled study $n = 64$	norm on ≥2 tests, or ≥2 SD below norm on 1 test.	if on ART. CD4 count: not specified VL: not specified	HIV-associated cognitive–motor impairment		completed the study on the original dose of medication.	Race/Ethnicity: 52% white Education (mean): 14 years Duration HIV+ (mean): 7.9 years CD4 count (mean): 262 cells/mm^3 CD4 nadir: not reportedLog10 Plasma VL (mean): 3.6 copies/mL Injection drug use: not reported Karnofsky Score (mean): 83	
l.D-Ala$_1$-peptide T-amide (DAPTA, or Peptide T) (Heseltine et al.)[37] Randomized, double-blind, placebo-controlled study $n = 215$	Cognitive dysfunction: ≥1.5 SD below norm on ≥2 tests, or ≥2.5 SD below mean on 1 test. Severe dysfunction: ≥1.5 SD below norm on ≥2 tests, one of which was ≥2.5 SD below norm	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) CD4 count: not specified, stratified on count (<200, 200–500, >500 cells/mm^3) VL: not specified	Determine whether intranasal peptide T improves cognitive function in HAND	Dose and route (intranasal) based on previous data from limited PK and Phase I studies	6-month change global neuropsychological z-score summarizing 23 measures	HAND: 66% severe deficit Sex: 95% male Age: 57% 18–39 years Race/Ethnicity: 82/5% white/black Education (mean): 15 years Duration HIV+ (mean): not reported CD4 count (mean): 53% with ≤200 cells/mm^3 CD4 nadir: not reported Plasma VL: not reported Substance Abuse: 56% previous use Karnofsky Score: not reported	6 months
l1.D-Ala$_1$-peptide T-amide (DAPTA, or Peptide T) (Goodkin et al.)[38] Retrospective substudy of above randomized, double-blind, placebo-controlled study[27] $n = 92$ (for CSF studies), $n = 57$ (for peripheral studies)	As above[29]	As above[29]	Examine if intranasal DAPTA is associated with a reduction in CSF and peripheral VL among a subgroup of participants enrolled in the study above[37]	As above[29]	6-month change in CSF and peripheral VL	*CSF VL Studies*[5]: HAND: 58% severe deficit Sex: 98% male Age (mean): 40 years Race/Ethnicity: 85/4% white/black Education (mean): 15.2 years Duration HIV+: not reported CD4 count: 45% with ≤200 cells/mm^3 CD4 nadir: not reported Plasma VL: not reported Substance Abuse: 61% previous use Karnofsky Score: not reported	6 months
m.Lexipafant (Schifitto et al.)[39] Randomized, double-blind, placebo-controlled study $n = 30$	Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test. Global impression	HAND: Any cognitive impairment. Ages: not specified ART: stable regimen for ≥6 weeks CD4 count: not specified VL: not specified	Assess the safety and tolerability, of lexipafant in HAND	Not discussed	Whether or not the subjected completed the study on the original dose of medication.	HAND: Global impression: 7/50/37/7% normal/mild/moderate/severe impairment Sex: 73% male Age (mean): 42.6 years Race/Ethnicity: 43% white Education (mean): 13.4 years	10 weeks

(*Continued*)

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
	of cognitive function assessed by neuro-psychologist, does not exclude abnormal NP test scores					Duration HIV+ (mean): 6.5 years CD4 count (mean): 390 cells/mm^3 CD4 nadir: not reported Plasma VL: not reported Illicit drug use: none reported during trial Karnofsky Score (mean): 81	
n.OPC-14117 (The Dana Consortium 1997)[40] Randomized, double-blind, placebo-controlled study *n* = 30	MSK staging Cognitive impairment: ≥1 SD below norm on ≥2 tests, or ≥2 SD below norm on 1 test.	HAND: Any cognitive impairment Ages: not specified ART: stable regimen for ≥6 weeks CD4 count: not specified VL: not specified	Assess the safety and tolerability of OPC-14117	Not discussed	Whether or not the subjected completed the study on the original dose of medication.	HAND: 53/47% ADC 0.5/1 Sex: 83% male Age (mean): 41.7 years Race/Ethnicity: 57/37% white/black Education (mean): 13.5 years Duration HIV+ (mean): 5.3 years CD4 count (mean): 234 cells/mm^3 CD4 nadir: not reported Plasma VL: not reported Illicit drug use: none reported during trial Karnofsky Score (mean): 85	12 weeks

HAND, human immunodeficiency virus-associated neurocognitive disorder; MND, mild neurocognitive disorder; ART, antiretroviral therapy; VL, viral load; MSK, Memorial Sloan Kettering.

[a]Uganda Neuropsych Test Battery Summary Measure: Grooved Pegboard dominant and nondominant hand, Color Trails 1 & 2, Symbol Digit Test, WHO-UCLA Verbal Learning test trial 5 total, WHO-UCLA Verbal Learning Test delayed recall, Digit Spans forwards and backwards.

[b]NPZ8: Trail Making Test parts A and B, Grooved Pegboard Test with dominant and nondominant hand, CalCAP Choice and Sequential Reaction Test Time, Timed Gait Test, Symbol Digit Test.

[c]NPZ6: Rey Auditory Verbal Learning (total number correct and delayed recall), Grooved Pegboard Test with dominant and non-dominant hand, CalCAP Choice and Sequential Reaction Time Test.

[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 Visuospatial 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].

[e]Peripheral VL Studies had a slightly different covariate mix, but are not presented here for the sake of brevity.

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

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

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 + ≥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 ≥1.5 SD below norm on ≥2 tests, or ≥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 Criteria (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
American 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 *cognitive* 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]Impairments 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 (l) and (l1) 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" trials[26] 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.

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Author Contributions

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Conflict of Interest

None declared.

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