

Substance abuse, hepatitis C, and aging in HIV: common cofactors that contribute to neurobehavioral disturbances

Randi Melissa Schuster¹
Raul Gonzalez²

¹Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA;

²Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

Abstract: Although the prevalence of neurocognitive disturbances among individuals with HIV has decreased in recent years, rates of impairment still remain high. This review presents findings on comorbid conditions that may contribute to further neurocognitive impairments in this already vulnerable population. The authors will focus on three cofactors that have received substantial attention in the neuroAIDS literature: drug use, hepatitis C virus (HCV) coinfection, and aging. All three conditions commonly co-occur with HIV and likely interact with HIV in complex ways. Collectively, the extant literature suggests that drug use, HCV, and aging serve to worsen the neurocognitive profile of HIV through several overlapping mechanisms. A better understanding of how specific comorbidities interact with HIV may reveal specific phenotypes of HIV-associated neurocognitive disorder that may aid in the development of more effective behavioral and pharmacological treatment efforts.

Keywords: drug use, neurocognition, HIV cofactors; HIV-associated neurocognitive disorder (HAND)

Introduction

Since the advent of combined antiretroviral therapy (cART) in 1996, there has been a decrease in the percentage of individuals living with HIV who experience dementia;^{1,2} however, current estimates suggest that between 15% and 50% of patients with HIV continue to experience neurocognitive impairment.^{1,3,4} Importantly, significant functional impairments are observed with HIV-associated neurocognitive disorder (HAND) and these include problems with medication adherence, driving, and finance management.⁵⁻⁸ These impairments serve to worsen the quality of life for patients with HIV and they may have significant adverse health and economic outcomes.⁹

Patterns of neurocognitive impairments among individuals with HIV typically include deficits in the domains of processing speed, memory, motor, and executive functioning.^{10,11} These impairments reflect abnormalities in prefrontal-striatal regions and connecting white matter.¹²⁻¹⁵ However, brain abnormalities are not circumscribed to these regions alone, as several studies show neuropathology and abnormal brain function in other areas, including the cerebellum and hippocampus.¹⁶⁻¹⁹

When considering HAND prevalence rates, it is important to note that the HIV-seropositive (HIV+) population comprises a heterogeneous group of individuals whose demographics have shifted throughout the course of the HIV epidemic. The disease now affects individuals with a broad range of ages, ethnicities, and socioeconomic statuses. Along with nonuniform demographic profiles, the types of comorbid conditions present among individuals in this population may vary substantially. More than two decades

Correspondence: Raul Gonzalez
Department of Psychiatry, University of Illinois at Chicago, 1601 W Taylor Street, MC912, Chicago, IL 60612, USA
Tel +1 312 413 5956
Fax +1 312 413 8147
Email rgonzalez@psych.uic.edu

of neuroAIDS research have revealed that several common comorbid factors are relevant in influencing the impact that HIV may have on neurobehavioral functioning. This review focuses on three such factors – drug use, hepatitis C virus (HCV) coinfection, and aging – which have received substantial attention in the neuroAIDS literature. These cofactors have high rates of co-occurrence with HIV, they have independent adverse influences on neurocognition, and they overlap to some extent in their neuropathology.

HIV and co-occurring substance use

Substance use is often a vector for HIV, either directly through injection drug use or indirectly through increased engagement in risky sexual behaviors. Thus, it is not surprising that nearly half of adults with HIV have a comorbid substance use disorder.^{20,21} Current research findings generally suggest that substance use among those with HIV serves as an additive risk factor for neurocognitive impairment. Substances may interact with HIV through multiple complex mechanisms, including modulation of proinflammatory cytokines, oxidative stress, perturbation of dopaminergic signaling, worsening immune function, and compromising the blood–brain barrier (BBB). In this review, the authors discuss these mechanisms and the neurocognitive deficits typically observed across various substances that have been studied in the context of HIV.

The authors have also distilled key pieces of information from these studies and have presented them in Tables 1–5, organized by substance. As is typically the case with such endeavors, it was not possible to include all relevant information regarding a study; several judgment calls needed to be made regarding the type and format of information that was ultimately included. Across all of the tables, the authors included only studies that clearly had samples of substance users who primarily used the substance of focus for that section of the table. This was particularly challenging for opioids, since many of the studies of opioid users included samples that might have also injected cocaine or might have used significant amounts of other drugs. Finally, the authors highlighted neurocognitive domains in the study when evidence for additive or synergistic effects were found – sometimes such effects were not tested. Interested readers should refer to the original manuscripts for details on a given study.

Opioids

Although the incidence of HIV transmission among injection drug users (IDUs) has stabilized since 2000, injection drug use (IDU) represents the second-highest risk factor for HIV

infection, accounting for 12% of new annual HIV infections, 19% of persons living with HIV, and 36% of AIDS cases.^{22–24} It is estimated that approximately three million IDUs are living with HIV, with the proportion of HIV+ IDUs as high as 40% in some countries. Of further significance, IDU confers increased risk for medication nonadherence and mortality among those with HIV.²⁵ By far, opioids (specifically, heroin) is the class of drugs most commonly used among IDUs;²⁶ however, it is important to note that injection of other substances including cocaine and methamphetamine (alone or in combination with heroin) is also common. Although most of the studies involving IDUs described in this review (Table 1) included a sample that consisted primarily of opioid users, some of the sample descriptions were not detailed enough to make this determination unequivocally. The authors opted to include such studies in the opioid section of this review based on epidemiological support, but the authors caution readers that the ability to generalize across these investigations may be limited by heterogeneous samples that might have been injecting other substances (most likely cocaine) in addition to opioids.

The principal manner by which opioids may exacerbate neurobehavioral disturbances in HIV is through their potent immunosuppressive effects,^{27,28} but the specific mechanisms by which this occurs are not well understood.²⁹ Studies with nonhuman primate models of HIV have found that morphine is linked with markers of increased disease progression,³⁰ modulation of cytokines, a blunted cell-mediated immune response, increased viral replication, and susceptibility to opportunistic infections.³¹ Others have similarly found evidence for opioids enhancing viral replication,^{32,33} reducing the effectiveness of CD4 and CD8 T-lymphocyte cells against HIV,^{34,35} and enhancing the likelihood of developing HIV encephalitis.^{36–38} Although the adverse effects of opioids on immune functioning have been extensively documented,^{27,28} others have suggested evidence for neuroprotective effects^{39,40} or no effect at all.⁴¹ Potential opposing mechanisms of opioids on HIV have been investigated in greater detail by others.^{42,43}

Neurobehavioral impairments among opioid users with HIV have often relied on samples of IDUs who primarily use heroin. In general, investigations have found a higher prevalence of dementia and global cognitive impairment among IDUs with HIV than among individuals with only one risk factor.^{44–46} HIV+ opioid users have also evidenced specific neurocognitive deficits, most reliably noted in the domains of attention, information processing, problem solving, working memory, and psychomotor speed.^{47–49} These deficits appear to persist even among HIV+ individuals who are asymptomatic^{50–52} and

Table 1 Studies examining opioid use, HIV, and neurocognitive impairment

Study	Sample	Substance use characteristics				Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
		Sample sizes	Frequency/amount of use	Duration of use					
Applebaum et al ⁴⁷	Opioid-dependent outpatients in MMT	HIV+, 80; HIV-, 80	NR	NR		NR	M CD4: 384.6 M plasma VL: 4311.9	G, AE, DM, SIP, V, VC	HIV+ were more impaired than HIV-
Ayuso-Mateos et al ⁵⁰	IDU outpatients at the HIV hospital clinic	HIV+, 65; HIV-, 49	NR	≈ 10 years		NR	M CD4: 439.2 Stage A (n = 41) and B (n = 24)	RT	HIV+ were more impaired on measures of simple and sequential reaction time
Bell et al ⁴⁴	Edinburgh cohort of AIDS patients	HM/HIV+, 35; IDU/HIV+, 45	NR	NR		NR	% HIVE: HM/HIV+, 17; IDU/HIV+, 56	G	IDU/HIV+ showed a higher prevalence of dementia
Del Pesce et al ⁵¹	Mixed community sample	IDU/Asy, 21; IDU/PGL, 18; IDU/HIV-, 30	≈ 3 times/week	≈ 8.8 years		≥ 3 months	M CD4: 809, Asy; 587, PGL	AE, DM, RT, SIP, V	Both HIV+ groups were more impaired than IDU/HIV-
McKegney et al ⁵³	Patients in MMT; past participants of The Prevalence Survey	HIV+, 83; HIV-, 137 (baseline)	NR	NR		NR	NR	AE, DM, MT, SIP, V	HIV+ were more impaired than HIV-
Rodriguez Salgado et al ⁵²	Male Spanish heterosexual polysubstance-using IDUs with history of opioid dependence	In MMT: IDU/HIV+, 21; IDU/HIV-, 21; not in MMT: IDU/HIV+, 33; IDU/HIV-, 27; controls, 23	NR	Addicted M ≈ 9.7 years		≥ 3 months	Asy, half with detectable plasma VL	G	HIV+ were more impaired than HIV-; those on MMT performed most poorly
Silberstein et al ⁵⁴	Patients in MMT; past participants of The Prevalence Survey	HIV+, 70; HIV-, 141	NR	NR		NR	NR	AE, DM, MT, SIP, V	HIV+ were more impaired than HIV-
Starace et al ⁴⁶	Outpatients from Italian Multicentre Neuropsychological HIV Study	IDU/HIV+, 75; IDU/HIV-, 97; controls, 79	NR	≥ 2 years		50% used heroin ≥ 1 week in past 30 days	Asy	G, AE, DM, MT, SIP, V	IDU/HIV+ were most impaired

Note: Bolded items indicate domains of significant impairment from both risk factors.

Abbreviations: AE, abstraction/executive; Asy, asymptomatic; DM, declarative memory; G, global; HIV-, HIV seronegative; HIV+, HIV seropositive; HIVE, HIV encephalitis; HM, homosexual men; IDU, injection drug use; M, mean; MMT, methadone maintenance therapy; MT, motor; NR, not reported; PGL, persistent generalized lymphadenopathy; RT, reaction time; SIP, speed of information processing; V, verbal/language; VC, visuospatial/constructional; VL, viral load.

Table 2 Studies examining cocaine (Coc) use, HIV, and neurocognitive impairment

Study	Sample	Substance use characteristics				Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
		Sample sizes	Frequency/amount of use	Duration of use					
Durvasula et al ⁹⁵	Gay/bisexual urban-dwelling African American men from African American Health Project	SyHIV, 95; AsyHIV, 67; HIV ⁺ , 75	28.7% non-cocaine users; 27% past users (>12 months ago); 24.9%, infrequent users (<1 use/week); 19.4%, frequent users (>1 use/week)	NR		84% negative toxicology	NR	AE, DM, MT, RT, SIP, WM, V, VC	Only main effects for Coc and serostatus; no interactions or tests of additive effects
Levine et al ⁹⁸	Mixed community sample of HIV ⁺	RSU, 17; NSU, 23	M = 14.7 days in past 30	NR		NR	M CD4: RSU, 361; NSU, 504 M plasma VL: RSU, 28,754; NSU, 3131 % AIDS: RSU, 62.5; NSU, 52.2	WM	RSU had more impaired sustained attention (ie, total omissions and reaction time variability) than NSU
Martin et al ⁹⁷	Men with high rates of cocaine abuse Chicago community and an urban Veterans Affairs Medical Center	HIV ⁺ , 41; HIV ⁻ , 37	Greater % of HIV ⁻ than HIV ⁺ used heroin, were IDUs and were on methadone	NR		NR	% Asy: 21; M CD4: 353 Md plasma VL: 1695	WM	HIV ⁺ were more impaired on auditory WM than HIV ⁻ ; deficits were equivalent at all disease stages
Meade et al ⁹⁶	Mixed HIV ⁺ community sample	Coc ⁺ , 25; Coc ⁻ , 39	M = 6.6 days in past 30	M = 18.1 years		NR	M CD4: Coc ⁺ , 539.2; Coc ⁻ , 701.1	G, AE, DM, SIP, V, VC	Coc ⁺ more impaired than Coc ⁻ ; G partially mediated the relationship between Coc use and medication adherence

Note: Bolded items indicate domains of significant impairment in group with both risk factors.

Abbreviations: AE, abstraction/executive; Asy, asymptomatic; Coc⁺, cocaine user; Coc⁻, cocaine non-user; DM, declarative memory; G, global; HIV⁺, HIV seropositive; IDU, injection drug use; M, mean; Md, median; MT, motor; NR, not reported; NSU, non-recent stimulant user (negative urine toxicology and no use in past 4 weeks); RSU, recent stimulant user (positive urine toxicology); RT, reaction time; SIP, speed of information processing; Sy, symptomatic; V, verbal/language; VC, visuospatial/constructional; VL, viral load; WM, attention/working memory.

Table 3 Studies examining methamphetamine (MA) use, HIV, and neurocognitive impairment

Study	Sample	Sample sizes	Substance use characteristics			Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
			Frequency/amount of use	Duration of use					
Carey et al ¹²⁸	HIV+ sample from HNRC group	MA+/IS, 200; MA+/NS, 47; MA-/IS, 55 MA-/NS, 160	≈1723 lifetime grams	≈12.1 years	≥10 days	Md plasma VL (log ₁₀): MA+/IS, 4.4; MA+/NS, 2.7; MA-/IS, 4.9; MA+/NS, 2.7 % AIDS: MA+/IS, 100; MA+/NS, 36; MA-/IS, 100; MA-/NS, 43 % HIVE: MA+, 100; MA-, 66.7	G, AE, DM, MT, SIP, V, WM	Additive effect of serostatus and immunosuppression on G	
Chana et al ¹¹⁸	Autopsies of HIV+ research participants from HNRC group	MA+, 8; MA-, 12	Abuse within 18 months prior to death	≥3 years of continuous use	NR		G, AE, DM, MT, SIP, V, WM	MA+ with HIVE were more impaired on G than MA- DM associated with neuronal loss; more neuronal loss in MA+ HCV, HIV, and MA independently associated with G	
Letendre et al ²⁶⁸	Mixed community sample from HNRC group	MA+/HIV+, 120; MA+, 119; HIV+, 119; control, 114	Dependence within past 18 months	NR	NR		G, AE, DM, MT, SIP, V, WM	Additive negative effects of MA and HIV status on neurocognitive impairment	
Rippeth et al ¹²⁷	Mixed community sample from HNRC group	MA+/HIV+, 43; MA+, 47; HIV+, 50; control, 60	% daily users: MA+/HIV+, 26; MA+, 49	≈11.7 years	≈5.2 months	M CD4: MA+/HIV+, 388; HIV+, 410 M plasma VL (log ₁₀): MA+/HIV+, 2.7; HIV+, 2.9 % AIDS: MA+/HIV+, 55; HIV+, 47	G, AE, DM, MT, SIP, V, WM		
Sadek et al ¹²⁹	Mixed community sample from HNRC group	MA+/HIV+, 86; MA+, 96; HIV+, 91; control, 89	≈2597 lifetime grams	≈11 years	≈90 days	M CD4: MA+/HIV+, 393; HIV+, 429 M plasma VL (log ₁₀): MA+/HIV+, 3.4; HIV+, 3.4 % AIDS: MA+/HIV+, 51; HIV+, 49	G, AE, DM, MT, SIP, WM	No differences between clinical groups G; all clinical groups more impaired than controls MA+/HIV+ more impaired than HIV+ on dichotomous G	

Note: Bolded items indicate domains of significant impairment in group with both risk factors.

Abbreviations: AE, abstraction/executive; DM, declarative memory; G, global; HCV, hepatitis C virus; HIV+, HIV seropositive; HIVE, HIV encephalitis; HNRC, HIV Neurobehavioral Research Center; IS, immunosuppressed (CD4 < 200); M, mean; MA+, methamphetamine user; MA-, methamphetamine non-user; NR, not reported; NS, nonimmunosuppressed (CD4 ≥ 200); SIP, speed of information processing; V, verbal/language; VL, viral load; WM, attention/working memory.

Table 4 Studies examining alcohol (Alc) use, HIV, and neurocognitive impairment

Study	Sample	Sample sizes	Substance use characteristics		Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
			Frequency/amount of use					
Durvasula et al ¹⁶¹	Community sample of men from African American Health Project	HD/HIV+, 31; MD/HIV+, 27; LD/HIV+, 81; ND/HIV+, 48; HD/HIV-, 49; MD/HIV-, 53; LD/HIV-, 112; ND/HIV-, 96	HD, ≥ 21 drinks/week; MD, 7–21 drinks/week; LD, < 7 drinks/week		NR	M CD4: HD/HIV+, 803.3; MD/HIV+, 769.8; LD/HIV+, 672.4; ND/HIV+, 723.9	AE, DM, MT, RT, SIP, WM, V, VC	Interactive effect; HD/HIV+ were more impaired than other seropositives and HD/HIV–
Fama et al ¹⁵⁶	Mixed community sample from the SRI Neuroscience Program	Alc+/HIV+, 47; Alc+, 38; HIV+, 40; control, 39 (baseline)	Lifetime kg about 880.9 (Alc+/HIV+, Alc+) and 51.9 (HIV+, control)		≈ 161 days	M CD4: Alc+/HIV+, 437.0; HIV+, 527.9 % AIDS: Alc+/HIV+, 32; HIV+, 25	DM, WM	Alc+/HIV+ performed worse on immediate memory than HIV+ and control
Green et al ¹⁵⁸	Gay and bisexual men	Alc+/HIV+, 21; Alc+, 12; HIV+, 29; control, 18	Past 12 month grams/week about 3.2 (Alc+/HIV+, Alc+) and 49.3 (HIV+, control)		NR	M CD4: Alc+/HIV+, 446.2; HIV+, 493.2	G, AE, DM, MT, RT, SIP, V, WM	Alc+/HIV+ performed worse than HIV+
Rothlind et al ¹⁵⁷	Mixed community sample from the SRI Neuroscience Program	HD/HIV+, 56; LD/HIV+, 70; HD/HIV-, 70; LD/HIV-, 72	Lifetime drinks/month about 179.2 (HD/HIV+, HD/HIV–) and 14.4 (LD/HIV+, LD/HIV–)		≥ 12 hours	M CD4: HD/HIV+, 373; LD/HIV+, 36 M plasma VL: HD/HIV+, 93,334; LD/HIV+, 79,927 % AIDS: HD/HIV+, 27; LD/HIV+, 39	AE, DM, MT, SIP, VC, WM	HIV+ heaviest drinkers most impaired
Sassoon et al ¹⁶⁰	Mixed community sample from the SRI Neuroscience Program	Alc+/HIV+, 55; Alc+, 44; HIV+, 43; control, 49	Lifetime kg about 868.5 (Alc+/HIV+, Alc+) and 54.3 (HIV+, control)		M ≈ 6 months	M CD4: Alc+/HIV+, 462.2; HIV+, 535.8 M plasma VL (log ₁₀): Alc+/HIV+, 3.2; HIV+, 3.0	AE, MT, SIP, VC	Alc+/HIV+ were most impaired
Schulte et al ¹⁵⁹	Mixed community sample from the SRI Neuroscience Program	Alc+/HIV+, 20; Alc+, 18; HIV+, 19; control, 19	Lifetime kg about 720.0 (Alc+/HIV+, Alc+) and 73.1 (HIV+, control)		M ≈ 8.5 months	M CD4: Alc+/HIV+, 511.3; HIV+, 495.6 M plasma VL: Alc+/HIV+, 13,010; HIV+, 11,311	AE, RT	Alc+/HIV+ were most impaired

Note: Bolded items indicate domains of significant impairment in groups with both risk factors.

Abbreviations: AE, abstraction/executive; Alc+, alcohol user; Alc–, alcohol non-user; DM, declarative memory; G, global; HD, heavy (or chronic) drinker; HIV+, HIV seronegative; HIV–, HIV seropositive; LD, light drinker; M, mean; MD, moderate drinker; MT, motor; ND, nondrinker; NR, not reported; RT, reaction time; SIP, speed of information processing; SRI, Stanford Research Institute; V, verbal/language; VC, visuospatial/constructional; VL, viral load; WM, attention/working memory.

Table 5 Studies examining cannabis (CAN) use, HIV, and neurocognitive impairment

Study	Sample	Sample sizes	Substance use characteristics			Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
			Frequency/amount of use	Duration of use					
Chang et al ²⁰²	Mixed community sample	CAN+/HIV+, 21; CAN+, 24; HIV+, 21; control, 30	≈16 days/month ≈197.1 lifetime grams	≈238.7 months	≈39.9 months	M CD4: CAN+/HIV+, 343.9; HIV+, 274.9 M plasma VL: CAN+/HIV+, 28,087; HIV+, 65,999	AE, MT, RT, SIP, V, WM	Negative additive effect of HIV and CAN on brain metabolites, but no additive or interactive effects on neurocognitive measures	
Cristiani et al ²⁰⁰	Mixed community sample	CAN+/SyHIV, 55; CAN+/AsyHIV, 79; SyHIV, 32; AsyHIV, 48; CAN+, 49; control, 25	≈326.2 uses/year	NR	NR	M CD4: CAN+/SyHIV,182.4; CAN+/AsyHIV,551.5; SyHIV, 272.7; AsyHIV, 520.6	G, AE, DM , MT, RT, SIP, V, VC, WM	Effects of CAN most prominent among SyHIV	
Gonzalez et al ²⁰¹	Polysubstance users from Chicago community and an urban Veterans Affairs Medical Center	CAN+/HIV+, 17; CAN+, 23; HIV+, 25; control, 21	NR	NR	NR	18% AIDS Md CD4: 366 48% had undetectable plasma VL	MT , PL	Additive effects; CAN+/HIV+ were more impaired than CAN+, HIV+, and controls	

Note: Bolded items indicate domains of significant impairment in groups with both risk factors.

Abbreviations: AE, abstraction/executive; Asy, asymptomatic; Can+, cannabis user; Can-, cannabis non-user; DM, declarative memory; G, global; HIV+, HIV seropositive; M, mean; Md, median; NR, not reported; PL, procedural learning; RT, reaction time; SIP, speed of information processing; Sy, symptomatic; V, verbal/language; VC, visuospatial/constructional; VL, viral load; WM, attention/working memory.

among those in methadone maintenance therapy.^{53,54} Margolin et al⁵⁵ carefully controlled for numerous potential confounds (sociodemographics, medical and psychiatric illnesses) and still found evidence to suggest that long- and short-term heroin and other drug use variables (eg, severity of drug use problems, current methadone use, positive urine toxicology) accounted for variance in neuropsychiatric impairment. Additionally, neurocognitive dysfunction typically observed in HIV+ populations that inject opioids is linked to clinically important functional outcomes such as medication nonadherence.^{56,57} However, results are not always consistent.⁵⁸ Some studies show only HIV serostatus to be a significant predictor of neuropsychological performance,^{59–61} while others demonstrate that the synergy between opioid use and HIV infection is weak, at best, after controlling for other potential neurocognitive confounds (eg, acute intoxication, vascular insults).⁶²

Cocaine

Cocaine (Table 2) is one of the most commonly abused drugs among HIV+ individuals,^{63,64} with epidemiological studies suggesting a higher incidence of HIV infection among those who abuse cocaine.⁶⁵ Overall, cocaine users are at a heightened risk for poorer HIV-related outcomes; however, evidence for additive or synergistic neurocognitive impairment from cocaine and HIV is mixed.

Cocaine is hypothesized to worsen the course of HIV through the modulation of cytokine production, subsequent disruption of immune functioning, neuroinflammation, and compromising cerebrovasculature, thereby rendering HIV+ individuals more susceptible to opportunistic infections and greater viral replication.³⁹ Both animal and human studies demonstrate the ability of cocaine to alter the secretion of immunoregulatory cytokines.^{66,67} Cocaine has also been shown to inhibit the secretion of various cytokines by peripheral blood lymphocytes and endothelial cells.^{68,69} The influence of cocaine on cytokine production has been associated with suppressed immune response, increased viral replication, and accelerated disease progression.^{70–72}

Both cocaine and HIV proteins (eg, tat and gp120) are independently toxic to dopamine neurons,^{39,73} and it is suggested that cocaine may aggravate the neurotoxic effects of HIV proteins in dopaminergically innervated brain regions such as the prefrontal cortex and striatum.^{39,74–76} For instance, cocaine has been shown to increase tat-mediated oxidative stress in rat hippocampal cell cultures *in vitro*.⁷⁷ Similarly, acute exposure to tat, gp120, and cocaine was shown to yield increased neurotoxicity, as indexed via changes in mitochondrial membrane potential and neuronal cell death.⁷⁸

Cocaine may exert a putative effect on HIV disease progression by compromising the integrity of the BBB. An intact BBB is important to limit infected cells from crossing into the central nervous system (CNS), infecting microglia, and causing an inflammatory response.⁷⁹ Not surprisingly, increased BBB permeability is associated with accelerated disease progression and is characteristic of the brains of AIDS patients with advanced and diffuse neurocognitive disturbances such as HIV-associated dementia.^{80–82} A number of different mechanisms for the adverse effects of cocaine on the BBB have been postulated.^{83,84} For example, cocaine and HIV proteins may damage the microvasculature of endothelial cells through downregulation of tight junction proteins, resulting in increased microvascular permeability of the BBB.^{80,85–87} Various cytokines that may be potentiated through cocaine administration can also be detrimental to BBB integrity.⁸⁸ Furthermore, cocaine-mediated upregulation of adhesion molecules expressed on the surface of endothelial cells may result in increased adhesion and transmigration of monocytes into the CNS.⁸⁷

Much less is known about the combined effects of HIV and cocaine on brain functioning, despite the wealth of information on their independent effects. It is reasonable to hypothesize that the co-occurrence of HIV and cocaine use would aggravate dysfunction in brain structures known to be preferentially affected by each, such as structures along prefrontal-striatal circuits.^{89,90} Despite this, evidence for synergistic effects is mixed. For instance, a preclinical investigation found that cocaine did not contribute to the pathological characteristics of HIV encephalitis (eg, astrogliosis and microgliosis) in HIV-infected mice.⁹¹ In contrast, Yao and colleagues⁹² found a synergistic effect between cocaine and gp120 that resulted in dendritic swelling and spine loss in rat hippocampal cell cultures. Chang and colleagues⁹³ found that individuals with HIV showed decreased dopamine transporter (DAT) density in the putamen and in the caudate, regardless of cocaine history. However, Meade and colleagues⁹⁴ showed that chronic cocaine dependence among HIV patients was associated with bilateral frontoparietal cortical hypoactivation during a delay-discounting task as compared with nonusing HIV patients, indicative of a less efficient use of cognitive resources.

Studies focusing on the conjoint influence of HIV and cocaine on neuropsychological test performance have also yielded equivocal results. Durvasula and colleagues⁹⁵ found only independent influences of HIV and recent cocaine use on psychomotor speed, but no interactions in a sample with relatively modest amounts of cocaine use. In contrast,

cocaine use was reported to magnify deficits in global cognitive functioning, verbal memory, processing speed, and visuospatial construction, which partially mediated the link between cocaine use and functional outcomes, among those with HIV.⁹⁶ In a sample comprised primarily of past cocaine users, deficits in auditory working memory were observed among those with HIV regardless of disease stage.⁹⁷ Levine et al⁹⁸ found that cocaine compounded the adverse effects of a positive HIV serostatus among a sample with a history of stimulant use (primarily cocaine), resulting in slower processing speed and poorer sustained attention.

Methamphetamine

Methamphetamine use (Table 3) and HIV frequently co-occur, particularly among men who have sex with men (MSM),^{99,100} with over 10% of HIV+ MSM in New York and San Francisco reporting having used methamphetamine in the previous 3 months.¹⁰¹ Methamphetamine use is also associated with increased engagement in high-risk sex, thereby increasing the chances for viral transmission and reinfection with a heterologous HIV strain (ie, HIV superinfection).^{102–104} Like cocaine, methamphetamine is also a psychostimulant that may worsen brain injury among HIV-infected individuals through similar mechanisms: immunosuppression, cerebrovascular injury, neurotoxicity, and inflammation.¹⁰⁵

Preclinical studies suggest that methamphetamine may potentiate brain injury in the context of HIV through modulation of cytokine production, inflammation, and further suppression of immune function. Dose-dependent adverse effects of methamphetamine on viral load and cytokine production have been shown through *in vitro* studies.¹⁰⁶ Indeed, a variety of different HIV-comparable animal models have shown that methamphetamine is linked to poorer immune functioning and increased viral burden in HIV.^{107,108} Cytokine levels were found to be significantly elevated in the striatum in mice who were infected with HIV and co-treated with methamphetamine.¹⁰⁹ Simian immunodeficiency virus (SIV)-infected rhesus macaques who were administered methamphetamine showed increased brain viral levels and heightened activation of natural killer cells as compared with controls.¹¹⁰

Methamphetamine may also compound the brain injury in HIV through cerebrovascular insults, including microinfarcts and vasoconstriction.^{111,112} Methamphetamine synergistically magnifies oxidative stress from viral proteins and decreases antioxidants in the brain, thus damaging membrane proteins and lipids in a manner that results in decreased tight junction protein expression and a weakened BBB.¹¹³ Mahajan et al¹¹⁴ found independent and synergistic influences of gp120 and

methamphetamine on the modulation of endothelial tight junctions, resulting in hyperpermeable BBB and increased transmigration of toxins and infected leukocytes.

Methamphetamine may also potentiate HIV-associated neurotoxicity. This appears to take place through mechanisms similar to those of cocaine; that is, through oxidative stress and neurotoxicity, with striatal dopaminergic neurons most susceptible to injury.^{109,115,116} Several *in vitro* and *in vivo* investigations of rodents and nonhuman primates with intrastratial or intrahippocampal tat injections have shown that methamphetamine administration resulted in multiplicative neurodegeneration, involving decreased dopamine levels, increased microglial activation, and more oxidative stress.^{109,117} Dopaminergic neurodegeneration and reduced DAT binding are even observed with low doses of methamphetamine and tat.¹¹⁵ Data from postmortem human tissue investigations support interactive effects of methamphetamine and HIV resulting in neuronal injury and accelerated programmed cell death, particularly in the brains of patients with HIV encephalitis.^{118–120} Cai and Cadet¹²¹ exposed cells to tat and methamphetamine alone and found no toxic effects, but their co-treatment resulted in increased cell death. Similarly, Langford et al¹¹⁶ showed that the co-treatment of methamphetamine and tat in hippocampal neurons resulted in decreased neuronal survival, increased oxidative stress, and dysregulated mitochondrial calcium potential. These investigations provide compelling evidence that methamphetamine and HIV proteins exert interactive neurotoxic effects.

Neuroimaging studies suggest that HIV and methamphetamine may augment brain injury, but the effects appear to be additive rather than synergistic.^{122,123} Interestingly, HIV and methamphetamine may exert overlapping but opposite influences on cortical brain volumes.¹²⁴ HIV was associated with decreased volumes and methamphetamine was associated with increased volumes in structures of the basal ganglia and cortex. The increased volume associated with methamphetamine use was thought to reflect abnormal dendritic pruning and sprouting.^{124,125} Ances et al¹²² examined the interaction between HIV and methamphetamine on cerebral blood flow in response to a finger-tapping paradigm within the lenticular nucleus, a component of the basal ganglia containing high concentrations of dopaminergic terminals. Significant main effects (but no interaction) for HIV infection and methamphetamine were found, with both independently associated with lower cerebral blood flow and greater changes in cerebral blood flow in response to the task. Taylor and colleagues¹²⁶ found that the relationship between viral load and abnormal cerebral metabolites in frontal gray matter

and basal ganglia was more pronounced in individuals who abused methamphetamine than in those who did not, suggesting that methamphetamine may exaggerate the damaging effects of HIV on neuronal integrity.

Methamphetamine use among those with HIV has been associated with poorer neurocognitive outcomes. In general, HIV+ methamphetamine users show more pronounced global cognitive deficits than HIV+ individuals without a history of methamphetamine use.¹²⁷ Executive functioning, motor skills, and learning appear to be the domains most sensitive to additive HIV and methamphetamine effects.^{127,128} Chana and colleagues¹¹⁸ found that methamphetamine users with HIV had greater degeneration of interneurons in the frontal cortex than those without a history of methamphetamine use at the time of death, which was associated with greater premorbid global and memory impairment. More studies are needed on how comorbid HIV and methamphetamine may affect everyday functioning, but current findings do not suggest compounding effects on functional outcomes.¹²⁹

Alcohol

Rates of alcohol use (Table 4) are significantly higher among HIV+ individuals than those in the general population,¹³⁰ with rates of alcohol use disorders estimated to be between two and four times higher in those with HIV.^{131–133} Heavy alcohol use among those with HIV is associated with decreased medication adherence,¹³⁴ health care utilization,¹³⁵ and overall survival,¹³⁶ along with increased HIV risk behaviors.^{137,138} As with the other substances covered in this review, alcohol is thought to interact with HIV through cytokine modulation, adverse effects on immune functioning, oxidative stress, damage to cerebrovasculature, and neurotoxicity.¹³⁹

Although the immunomodulatory effects of alcohol are a subject of contention in the literature,¹⁴⁰ most evidence suggests alcohol exerts adverse effects on the immune functioning of those with HIV. Both chronic and acute alcohol consumption are thought to increase inflammatory responses, viral replication, and susceptibility to opportunistic infections in both murine and human models of HIV.^{141,142} Chronic ethanol administration has been shown to upregulate cytokines in the cerebral cortex of mice.¹⁴³ Even a single, acute administration of alcohol was associated with increased susceptibility to pathogens through attenuation of tumor necrosis factor alpha.¹⁴⁴ In SIV-infected macaques, alcohol exposure is associated with increased viral load,^{145,146} increased proinflammatory cytokines,¹⁴⁷ impaired immune response,¹⁴⁸ and, ultimately, accelerated disease progression.

Alcohol may also serve to exacerbate HIV-associated neurotoxicity, presumably through oxidative stress, resulting in enhanced neuronal injury and apoptosis. This is supported by animal models showing that ethanol administration leads to greater oxidative stress and protein oxidation of gp120 than saline administration.¹⁴⁹ In vitro studies of human brain microvascular endothelial cells showed that co-treatment of HIV proteins and alcohol was associated with a synergistic increase in apoptosis of endothelial cells,¹⁵⁰ resulting in decreased structural integrity of the BBB and augmented neuroinvasion and HIV proliferation in the brain.^{151,152}

Neuropathology and neuroimaging studies investigating the combined effects of chronic alcohol use and HIV infection generally show enhanced abnormalities in the periventricular white matter, subcortical gray matter, and brain stem of alcohol users with HIV.¹⁴¹ Pfefferbaum and colleagues¹⁵³ found metabolic abnormalities in parietal-occipital gray matter and adjacent white matter in patients with a dual diagnosis of HIV and alcoholism, which were not present in cases of HIV or alcoholism alone. Additionally, alcohol may potentiate white matter hyperintensities in the corpus callosum and frontal regions.^{153,154}

Only a few studies to date have addressed the combined effects of alcohol use and HIV on neurocognitive functioning. The available evidence suggests that both quantitative (amount of use, frequency of use) and qualitative indices (abuse or dependence) of alcohol use exert independent, additive, and synergistic influences on neuropsychological functioning among those with HIV. The domains of attention, memory, and processing speed most consistently show signs of impairment.^{155–157} An interactive influence of HIV infection and alcohol was observed on measures of verbal reasoning, reaction time, and auditory information processing in a well-matched sample of patients stratified by their serostatus and history of alcohol use disorder – patients with HIV who abused alcohol showed the greatest signs of impairment.¹⁵⁸ Others reported that HIV alone was not associated with deficits in attentional processes, but was linked to deficits on Stroop performance when combined with alcohol abuse.¹⁵⁹ Interactive effects of HIV and alcohol have also been cited in the domains of psychomotor speed, attention, and learning using a modified version of the digit-symbol task.¹⁶⁰ However, the compounding influences of alcohol and HIV most consistently emerge among samples of heavy recent drinkers.^{157,161}

Cannabis

The influence of cannabis (Table 5) on HAND is an important phenomenon to consider, given the high rates of cannabis

use among HIV-infected populations^{162,163} and accumulating evidence supporting its medical value in mitigating some of the common symptoms of HIV.^{164–166} Delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis, exerts many of its psychoactive effects through modulation of signaling in the basal ganglia, prefrontal cortex, and hippocampus – structures commonly affected by HIV.^{167–169} Similar to HIV, neuroimaging data also show dysfunction of prefrontal-striatal and hippocampal structures in the context of cannabis use.^{170–172} Despite this, little remains known about how cannabis affects brain functioning among individuals with HIV.

Substantial preclinical evidence suggests that cannabis may be immunosuppressive and it may worsen the course of HIV. However, human studies yield equivocal results. Specifically, preclinical cellular and animal studies confirm that the active constituents of cannabis can suppress immune function,^{173,174} promote lymphocyte apoptosis,¹⁷⁵ promote tumor growth,¹⁷⁶ and increase HIV receptor expression and replication.¹⁷⁴ Evidence in support of the deleterious health influences of cannabis includes studies showing that among HIV+ patients, cannabis use is associated with more opportunistic infections,^{177–179} sexually transmitted diseases,¹⁸⁰ poorer overall health,¹⁸¹ increased HIV viral load,^{182,183} lower CD4 counts,¹⁸¹ and more rapid progression to AIDS.¹⁸⁴ Yet, others have failed to find relationships between cannabis use and increased risk of infection,^{185–187} more rapid progression to AIDS,^{188–190} or with immune biomarkers.^{182,191,192} The picture is further complicated by data showing that cannabinoids may be neuroprotective through inhibition of proinflammatory cytokine production.^{193–195} Recently, an *in vivo* experimental investigation of rhesus macaques found that THC ameliorated SIV progression, decreased mortality, and improved retention of body mass.¹⁹⁶

It is reasonable to suspect that the presence of both HIV and cannabis use may potentiate neurocognitive impairments, given that cannabis has also been shown to impair episodic memory and executive functioning.^{197–199} Cristiani and colleagues²⁰⁰ found evidence for an HIV-cannabis interaction, such that symptomatic HIV+ individuals who used cannabis exhibited the most global neuropsychological deficits, with memory most prominently impaired. Evidence of additive adverse effects of cannabis use on complex motor skills in abstinent HIV+ polysubstance users has also been reported.²⁰¹ Chang et al²⁰² used magnetic resonance spectroscopy to compare HIV+ cannabis users, HIV+ nonusers, cannabis users without HIV, and healthy controls and found evidence of negative additive effects of cannabis use and HIV for some

(but not all) metabolites in the basal ganglia and thalamus; however, there was no interaction between cannabis and HIV on neurocognitive functioning. Thus, current findings are mixed, but the available evidence leans toward supporting adverse effects of comorbid HIV and cannabis on neuropsychological performance.

HCV and HIV

Over 20% of those with HIV in the United Kingdom and Spain also have HCV coinfection,^{203,204} with dual diagnosis rates as high as 90% in London, Italy, and Australia for those with percutaneous exposure (eg, IDU).^{205–207} High rates of coinfection are problematic, given that the presence of both diseases is associated with poor outcomes.^{203,208–210} Both HIV and HCV are neuroinvasive, cross the BBB via infected leukocytes,^{211,212} and replicate in brain tissue.^{213–215} Given the high rates of comorbidity and the common routes of transmission and progression, a growing number of investigations have been devoted to examining the compounding effects on neuropsychological functioning in HIV-HCV coinfection.

Several mechanisms for how HIV and HCV may interact to affect brain functioning have been suggested, and are the topic of several prior reviews.^{218–221} Collectively, they suggest that cytokine modulation and neurotoxicity are key processes that likely contribute to more pronounced cognitive dysfunction among individuals with dual infections. There is evidence that HIV and HCV may enhance cytokine production and increase inflammatory response.^{222,223} Additionally, HCV may potentiate the effects of HIV neurotoxic proteins in microglia and astrocytes, leading to enhanced neuroimmune activation, suppression of neuronal autophagy, and, ultimately, cell death and overall neurodegeneration.²²⁴

The influence of HIV-HCV coinfection on neuropsychological functioning has also been reviewed.^{225–228} Although some studies suggest only independent adverse influences of HIV or HCV on neuropsychological functioning,^{14,229} the growing consensus is that coinfecting individuals fare worse on neuropsychological measures than monoinfected individuals or healthy controls, with additive influences seen primarily in the domains of executive functioning and processing speed.^{218,230–232} This trend emerges even when common comorbidities are carefully controlled. For example, Cherner and colleagues²³³ examined the unique impact of HIV, HCV, and methamphetamine use on neurocognitive profiles. They found evidence for increasing decrements in the domains of learning, recall, fine motor speed, and problem solving with the addition of each disorder, suggesting additive effects of HCV and HIV. In response to these published findings, van

Gorp and Hinkin²³⁴ underscored the importance of elucidating how risk for neuropsychological impairment increases in cases of HIV-HCV coinfection. The authors of this commentary highlighted the need for further investigations aimed at better understanding (1) how additional high-frequency cofactors (eg, drug/alcohol use, head injury, psychiatric illness) further compromise cognitive functioning and (2) how such cognitive deficits translate into functional impairment.

Aging and HIV

Those with HIV are living longer because of more effective and sophisticated regimens of cART, transforming the course of HIV infection from an acute, life-threatening illness into a manageable, chronic disease. Indeed, older patients comprise a growing segment of the infected population, with 25% of individuals with HIV and 32% of people with AIDS over 50 years of age in the United States.²³⁵ Additionally, rates of new infections among senior populations have also increased dramatically. In 2009, 16.5% of new HIV diagnoses and 23% of new AIDS diagnoses were made to patients over 50 years of age.²³⁵ Recent reports project that older adults will account for 50% of people living with HIV by 2015.²³⁶

Older patients with HIV are vulnerable to neurocognitive decline associated with normal aging, as well as to various medical complications that can emerge and which may worsen their neurocognitive health. They are more likely to develop Kaposi's sarcoma, which is linked with progressive age-related declines in immunocompetence and thymic activity.^{237–239} Importantly, thymic activity is associated with poor immune reconstitution, which is correlated with increased risk for AIDS and for other diseases.^{240–242} Similarly, older patients with HIV have a greater incidence of hypercholesterolemia, diabetes, and lower immuno-resiliency, all of which can further compromise neurocognitive functioning.²⁴³ Dendritic damage, axonal injury, and Alzheimer's-like plaque deposition in the hippocampus^{244,245} are also seen with aging and likely adversely affect neurocognition.

Both HIV and aging exert a similar pattern of effects on immune function, including an overall reduction in CD4 T cells, inversion of CD4:CD8 ratios, shorter telomere length of CD8 T cells, increased susceptibility to apoptosis, reduced capacity to proliferate mitogens, changes in cytokine production, and a shift to more maturely differentiated T cells.^{246–248} Not surprisingly, there is evidence for both additive and synergistic influences of HIV and aging on immunological perturbations and a subsequent acceleration in progression to AIDS.^{249,250} For instance, it was found that older age was associated with a depleted pool of naïve CD4 and

CD8 lymphocytes,²⁵¹ which is predictive of poorer immune reconstitution after treatment initiation.²⁵²

Neuroimaging studies suggest conjoint adverse effects of HIV and aging on brain structure and function. Ernst and Chang²⁵³ demonstrated that HIV infection resulted in a fivefold increase in inflammatory and glial metabolites in the basal ganglia, beyond what would be expected in normal aging. Using similar methodologies, Chang and colleagues²⁵⁴ showed independent, parallel effects of HIV and aging on metabolic markers in the basal ganglia and frontal white matter, suggestive of adverse additive influences on neuronal integrity and gliosis. However, the impact of HIV on neuronal integrity in frontal white matter appeared more prominent in younger HIV+ individuals than in older HIV+ individuals. HIV and aging have also been demonstrated to have similar pathophysiological effects in the visual cortex through the use of functional magnetic resonance imaging.¹²

Most of the current research findings suggest that aging is a risk factor for accelerated and more severe neurocognitive decline among those with HIV, as both conditions have been viewed as concomitant neurodegenerative processes,^{244,253,255} although some have reported no interactions.²⁵⁶ Researchers have cited rates of severe cognitive impairment (eg, dementia) up to three times higher in older HIV+ patients as compared with younger cohorts, although longer durations of viral infection among older adults may influence these findings.^{257–259} Cherner and colleagues²⁵⁵ conducted a cross-sectional investigation comparing HIV patients over the age of 75 with those under the age of 35. Cerebrospinal fluid (CSF) viral burden and age were both independently and interactively predictive of neurocognitive impairment, even after controlling for substance use and mental health confounds. Specifically, older adults with detectable CSF viral load were twice as likely to exhibit cognitive impairment as those without detectable viral load. Those with more advanced disease may be more susceptible to the negative influence of age on HAND.²⁶⁰ Others have suggested that aging with HIV may result in qualitatively different patterns of neurocognitive impairments.^{244,261} For instance, HIV+ older adults evidenced increasingly inconsistent performance across neurocognitive domains compared with younger individuals, thought to be reflective of increased injury to prefrontal-striatal circuits.²⁶² Genetic factors, such as the presence of the apolipoprotein E4 allele, may also increase risk of dementia among those aging with HIV.²⁵⁷ Importantly, HIV+ older individuals with cognitive impairment show greater emotional, psychosocial, and functional deficits (eg, medication adherence) than those without pronounced cognitive deficits.^{263,264}

Conclusion

The research findings presented in this review underscore the importance of considering what comorbid conditions commonly present among individuals with HIV. Clearly, substance use disorders, HCV coinfection, and even the age of the patient may have a significant impact on their neurocognition. Yet, the interactions of HIV with these comorbid factors are complex and not yet completely understood. Nonetheless, several potential mechanisms by which they may interact frequently occur in the literature and include immune suppression, damage to cerebrovasculature, oxidative stress, inflammation, and neurotoxicity.

Collectively, the evidence more frequently suggests additive adverse effects when HIV is present alongside the conditions covered in this review. However, it is important to consider that such studies are beset with significant challenges due to the high rates of additional comorbid conditions that tend to present with substance use disorders, HCV, and older age. For example, substance use is often accompanied by a high rate of additional comorbidities including head injury, cerebrovascular disorders, malnutrition, and a spectrum of psychiatric illnesses including mood disorders, anxiety disorders, post-traumatic stress disorder, psychosis, and attention-deficit/hyperactivity disorder, all of which will likely influence neurocognition.^{36,265,266} Similarly, HCV is often also associated with liver disease, depression, and lower education. Older age also has many associated medical conditions, including hypertension, hypercholesterolemia, diabetes, and higher prevalence of degenerative dementias. All of these may also affect neurocognition adversely. To further complicate matters, all of these risk factors (ie, substance use, HCV, and older age) may be present, singly or in combination, among the HIV+ samples of many of the studies the authors reviewed. The extent to which different studies assess and control for these additional risk factors varies substantially. Furthermore, the effects of polypharmacy (eg, psychotropics, opioid replacement therapy, cART) on neurocognitive outcomes remain understudied in combination with comorbid conditions. This contributes to significant heterogeneity that hampers comparisons across studies and, ultimately, limits the conclusions that can be drawn. Because of this, it is critical for future investigations to use a clear and comprehensive set of inclusion and exclusion criteria and carefully control for potential confounding variables, as well as to provide detailed data on the presence of these comorbidities in their sample.

The multitude of permutations of factors that may interact to affect neurocognition in HIV is daunting. Nonetheless,

the continually growing focus on how HIV interacts with comorbid conditions is a welcomed trend, especially when considering how often these disorders co-occur and how rarely their combined effects on neurocognition were studied historically. Much remains to be known about the interactions of other common systemic illnesses and HIV, the impact of drug-drug interactions and polypharmacy, and how aging with HIV may affect functional outcomes and the ability to live independently. Importantly, further refining understanding of the neurocognitive profiles of individuals with HIV with various comorbid conditions may help to identify specific HAND phenotypes, which will aid in the development of more specific treatments, both pharmacologically and behaviorally.

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