Neurobehavioral HIV Medicine

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REVIEW

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

This article was published in the following Dove Press journal:
Neurobehavioral HIV Medicine
14 February 2012
Number of times this article has been viewed

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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

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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	Sample sizes	Substance use characteristics					
			Frequency/ amount of use	Duration of use	Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
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	Sample sizes	Substance use characteristics					
			Frequency/ amount of use	Duration of use	Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
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 seronegative; 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.

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

Study	Sample	Sample sizes	Substance use characteristics					
			Frequency/ amount of use	Duration of use	Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
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	**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	% HIVE: MA+, 100; MA–, 66.7	**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+
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	NR	**G**, AE, DM, MT, SIP, V, WM	HCV, HIV, and MA independently associated with G
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**	Additive negative effects of MA and HIV status on neurocognitive impairment
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 that 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; Md, median; MT, motor; 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				
			Frequency/ amount of use	Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
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					
			Frequency/ amount of use	Duration of use	Length of abstinence	HIV disease characteristics	Domains assessed	Key findings
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 al[55] 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 colleagues[92] found a synergistic effect between cocaine and gp120 that resulted in dendritic swelling and spine loss in rat hippocampal cell cultures. Chang and colleagues[93] 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 colleagues[94] 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 colleagues[95] 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 al[98] 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: immunosupression, 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 al[114] 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 intrastriatal 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 Cadet[121] exposed cells to tat and methamphetamine alone and found no toxic effects, but their co-treatment resulted in increased cell death. Similarly, Langford et al[116] 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 al[122] 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 colleagues[126] 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 colleagues[118] 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 colleagues[153] 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 colleagues[200] 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 al[202] 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 coinfected 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 colleagues[233] 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 Hinkin[234] 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 Chang[253] 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 colleagues[254] 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 colleagues[255] 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.

Acknowledgments

The authors thank Inga Salija for her assistance with preparing the review. This publication was made possible by grants K23DA023560 (PI: Gonzalez) and F31DA032244-01 (PI: Schuster) from the National Institute on Drug Abuse (NIDA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIDA or the National Institutes of Health.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. 2011; 17(1):3–16.
2. Tozzi V, Balestra P, Bellagamba R, et al. Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. *J Acquir Immune Defic Syndr*. 2007;45(2):174–182.
3. Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. *J Neurovirol*. 2004;10(6):350–357.
4. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*. 2010; 24(9):1243–1250.
5. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc*. 2004;10(3):317–331.
6. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *J Neurovirol*. 2002;59(12):1944–1950.
7. Marcotte TD, Wolfson T, Rosenthal TJ, et al. A multimodal assessment of driving performance in HIV infection. *Neurology*. 2004;63(8): 1417–1422.
8. Thames AD, Becker BW, Marcotte TD, et al. Depression, cognition, and self-appraisal of functional abilities in HIV: an examination of subjective appraisal versus objective performance. *Clin Neuropsychol*. 2011;25(2): 224–243.

9. Munakata J, Benner JS, Becker S, Dezii CM, Hazard EH, Tierce JC. Clinical and economic outcomes of nonadherence to highly active antiretroviral therapy in patients with human immunodeficiency virus. *Med Care*. 2006;44(10):893–899.
10. Heaton RK, Grant I, Butters N, et al. The HNRC 500 – neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. *J Int Neuropsychol Soc*. 1995;1(3):231–251.
11. Reger M, Welsh R, Razani J, Martin DJ, Boone KB. A meta-analysis of the neuropsychological sequelae of HIV infection. *J Int Neuropsychol Soc*. 2002;8(3):410–424.
12. Ances BM, Vaida F, Yeh MJ, et al. HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. *J Infect Dis*. 2010;201(3):336–340.
13. Chang L, Speck O, Miller EN, et al. Neural correlates of attention and working memory deficits in HIV patients. *Neurology*. 2001;57(6):1001–1007.
14. Cohen RA, Harezlak J, Schifitto G, et al. Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. *J Neurovirol*. 2010;16(1):25–32.
15. Jernigan TL, Archibald S, Hesselink JR, et al. Magnetic resonance imaging morphometric analysis of cerebral volume loss in human immunodeficiency virus infection. The HNRC Group. *Arch Neurol*. 1993;50(3):250–255.
16. Castelo JM, Sherman SJ, Courtney MG, Melrose RJ, Stern CE. Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. *Neurology*. 2006;66(11):1688–1695.
17. Klunder AD, Chiang MC, Dutton RA, et al. Mapping cerebellar degeneration in HIV/AIDS. *Neuroreport*. 2008;19(17):1655–1659.
18. Moore DJ, Masliah E, Rippeth JD, et al. Cortical and subcortical neurodegeneration is associated with HIV neurocognitive impairment. *AIDS*. 2006;20(6):879–887.
19. Thompson PM, Dutton RA, Hayashi KM, et al. 3D mapping of ventricular and corpus callosum abnormalities in HIV/AIDS. *Neuroimage*. 2006;31(1):12–23.
20. Galvan FH, Burnam MA, Bing EG. Co-occurring psychiatric symptoms and drug dependence or heavy drinking among HIV-positive people. *J Psychoactive Drugs*. 2003;35(Suppl 1):S153–S160.
21. Rabkin JG, McElhiney MC, Ferrando SJ. Mood and substance use disorders in older adults with HIV/AIDS: methodological issues and preliminary evidence. *AIDS*. 2004;18 (Suppl 1):S43–S48.
22. Center for Disease Control and Prevention. Fact Sheet: Estimates of New HIV Infections in the United States. 2008; Available from: http://www.cdc.gov/hiv/topics/surveillance/resources/factsheets/pdf/incidence.pdf. Accessed August 4, 2011.
23. Center for Disease Control and Prevention. Fact Sheet: HIV and AIDS in the United States. 2010; Available from: http://www.cdc.gov/hiv/resources/factsheets/PDF/us.pdf. Accessed August 4, 2011.
24. Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*. 2008;372(9651):1733–1745.
25. Cohn SE, Jiang H, McCutchan JA, et al. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. *AIDS Care*. 2011;23(6):775–785.
26. Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2011. [Epub ahead of print.]
27. Brinkman WJ, Hall DM, Suo JL, Weber RJ. Centrally-mediated opioid-induced immunosuppression. Elucidation of sympathetic nervous system involvement. *Adv Exp Med Biol*. 1998;437:43–49.
28. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. *Am J Ther*. 2004;11(5):354–365.
29. Donahoe RM, Vlahov D. Opiates as potential cofactors in progression of HIV-1 infections to AIDS. *J Neuroimmunol*. 1998;83(1–2):77–87.
30. Kumar R, Torres C, Yamamura Y, et al. Modulation by morphine of viral set point in rhesus macaques infected with simian immunodeficiency virus and simian-human immunodeficiency virus. *J Virol*. 2004;78(20):11425–11428.
31. Bokhari SM, Hegde R, Callen S, et al. Morphine Potentiates Neuropathogenesis of SIV Infection in Rhesus Macaques. *J Neuroimmune Pharmacol*. 2011;6(4):626–639.
32. Peterson PK, Gekker G, Hu S, Lokensgard J, Portoghese PS, Chao CC. Endomorphin-1 potentiates HIV-1 expression in human brain cell cultures: implication of an atypical mu-opioid receptor. *Neuropharmacology*. 1999;38(2):273–278.
33. Schweitzer C, Keller F, Schmitt MP, et al. Morphine stimulates HIV replication in primary cultures of human Kupffer cells. *Res Virology*. 1991;142(2–3):189–195.
34. Quang-Cantagrel ND, Wallace MS, Ashar N, Mathews C. Long-term methadone treatment: effect on CD4+ lymphocyte counts and HIV-1 plasma RNA level in patients with HIV infection. *Eur J Pain*. 2001;5(4):415–420.
35. Wang AX, Li TS, Cao YZ, Han Y, Qiu ZF, Xie J. T-cell response of advanced aids patients after highly active antiretroviral therapy. *Chin Med Sci J*. 2005;20(4):223–225.
36. Bell JE, Donaldson YK, Lowrie S, et al. Influence of risk group and zidovudine therapy on the development of HIV encephalitis and cognitive impairment in AIDS patients. *AIDS*. 1996;10(5):493–499.
37. Davies J, Everall IP, Weich S, McLaughlin J, Scaravilli F, Lantos PL. HIV-associated brain pathology in the United Kingdom: an epidemiological study. *AIDS*. 1997;11(9):1145–1150.
38. Morgello S, Mahboob R, Yakoushina T, Khan S, Hague K. Autopsy findings in a human immunodeficiency virus-infected population over 2 decades: influences of gender, ethnicity, risk factors, and time. *Arch Pathol Lab Med*. 2002;126(2):182–190.
39. Nath A, Hauser KF, Wojna V, et al. Molecular basis for interactions of HIV and drugs of abuse. *J Acquir Immune Defic Syndr*. 2002;31(Suppl 2):S62–S69.
40. Spijkerman IJ, Langendam MW, Veugelers PJ, et al. Differences in progression to AIDS between injection drug users and homosexual men with documented dates of seroconversion. *Epidemiology*. 1996;7(6):571–577.
41. Thorpe LE, Frederick M, Pitt J, et al. Effect of hard-drug use on CD4 cell percentage, HIV RNA level, and progression to AIDS-defining class C events among HIV-infected women. *J Acquir Immune Defic Syndry*. 2004;37(3):1423–1430.
42. Everall IP. Interaction between HIV and intravenous heroin abuse? *J Neuroimmunol*. 2004;147(1–2):13–15.
43. Nath A. Human immunodeficiency virus-associated neurocognitive disorder: pathophysiology in relation to drug addiction. *Ann NY Acad Sci*. 2010;1187:122–128.
44. Bell JE, Brettle RP, Chiswick A, Simmonds P. HIV encephalitis, proviral load and dementia in drug users and homosexuals with AIDS. Effect of neocortical involvement. *Brain*. 1998;121(Pt 11):2043–2052.
45. Bouwman FH, Skolasky RL, Hes D, et al. Variable progression of HIV-associated dementia. *Neurology*. 1998;50(6):1814–1820.
46. Starace F, Baldassarre C, Biancolilli V, et al. Early neuropsychological impairment in HIV-seropositive intravenous drug users: evidence from the Italian Multicentre Neuropsychological HIV Study. *Acta Psychiatr Scand*. 1998;97(2):132–138.
47. Applebaum AJ, Otto MW, Richardson MA, Safren SA. Contributors to neuropsychological impairment in HIV-infected and HIV-uninfected opiate-dependent patients. *J Clin Exp Neuropsyc*. 2010;32(6):579–589.
48. Bartok JA, Martin EM, Pitrak DL, et al. Working memory deficits in HIV-seropositive drug users. *J Int Neuropsychol Soc*. 1997;3(5):451–456.
49. Wellman MC. Neuropsychological impairment among intravenous drug users in pre-AIDS stages of HIV infection. *Int J Neurosci*. 1992;64(1–4):183–194.
50. Ayuso-Mateos JL, Pereda M, Gomez Del Barrio A, Echevarria S, Farinas MC, Garcia-Palomo D. Slowed reaction time in HIV-1-seropositive intravenous drug users without AIDS. *Eur Neurol*. 2000;44(2):72–78.

51. Del Pesce M, Franciolini B, Censori B, et al. Cognitive behavior in asymptomatic (CDC stage II and III) HIV – seropositive intravenous drug users (IVDUs). *Ital J Neurol Sci*. 1993;14(9):619–625.
52. Rodriguez Salgado D, Rodriguez Alvarez M, Seoane Pesqueira G. Neuropsychological impairment among asymptomatic HIV-positive former intravenous drug users. *Cogn Behav Neurol*. 2006;19(2):95–104.
53. McKegney FP, O'Dowd MA, Feiner C, Selwyn P, Drucker E, Friedland GH. A prospective comparison of neuropsychologic function in HIV-seropositive and seronegative methadone-maintained patients. *AIDS*. 1990;4(6):565–569.
54. Silberstein CH, McKegney FP, O'Dowd MA, et al. A prospective longitudinal study of neuropsychological and psychosocial factors in asymptomatic individuals at risk for HTLV-III/LAV infection in a methadone program: preliminary findings. *Int J Neurosci*. 1987;32(3–4):669–676.
55. Margolin A, Avants SK, Warburton LA, Hawkins KA. Factors affecting cognitive functioning in a sample of human immunodeficiency virus-positive injection drug users. *AIDS Patient Care STDS*. 2002;16(6):255–267.
56. Avants SK, Margolin A, Warburton LA, Hawkins KA, Shi J. Predictors of nonadherence to HIV-related medication regimens during methadone stabilization. *Am J Addiction*. 2001;10(1):69–78.
57. Waldrop-Valverde D, Ownby RL, Wilkie FL, Mack A, Kumar M, Metsch L. Neurocognitive aspects of medication adherence in HIV-positive injecting drug users. *AIDS Behav*. 2006;10(3):287–297.
58. Hestad K, Aukrust P, Ellertsen B, Klove H, Wilberg K. Neuropsychological deficits in HIV-1 seropositive and seronegative intravenous drug users. *J Clin Exp Neuropsyc*. 1993;15(5):732–742.
59. Concha M, Selnes OA, Vlahov D, et al. Comparison of neuropsychological performance between AIDS-free injecting drug users and homosexual men. *Neuroepidemiology*. 1997;16(2):78–85.
60. Farinpour R, Martin EM, Seidenberg M, et al. Verbal working memory in HIV-seropositive drug users. *J Int Neuropsychol Soc*. 2000;6(5):548–555.
61. Selnes OA, McArthur JC, Royal W 3rd, et al. HIV-1 infection and intravenous drug use: longitudinal neuropsychological evaluation of asymptomatic subjects. *Neurology*. 1992;42(10):1924–1930.
62. Byrd DA, Fellows RP, Morgello S, et al. Neurocognitive Impact of Substance Use in HIV Infection. *J Acquir Immune Defic Syndr*. 2011;58(2):154–162.
63. Cook JA, Grey DD, Burke-Miller JK, et al. Illicit drug use, depression and their association with highly active antiretroviral therapy in HIV-positive women. *Drug Alcohol Depen*. 2007;89(1):74–81.
64. Korthuis PT, Zephyrin LC, Fleishman JA, et al. Health-related quality of life in HIV-infected patients: the role of substance use. *AIDS Patient Care STDS*. 2008;22(11):859–867.
65. Goodkin K, Shapshak P, Metsch LR, et al. Cocaine abuse and HIV-1 infection: epidemiology and neuropathogenesis. *J Neuroimmunol*. 1998;83(1–2):88–101.
66. Chen GJ, Watson RR. Modulation of tumor necrosis factor and gamma interferon production by cocaine and morphine in aging mice infected with LP-BM5, a murine retrovirus. *J Leuokocyte Biol*. 1991;50(4):349–355.
67. Pellegrino T, Bayer BM. In vivo effects of cocaine on immune cell function. *J Neuroimmunol*. 1998;83(1–2):139–147.
68. Mao JT, Huang M, Wang J, Sharma S, Tashkin DP, Dubinett SM. Cocaine down-regulates IL-2-induced peripheral blood lymphocyte IL-8 and IFN-gamma production. *Cell Immunol*. 1996;172(2):217–223.
69. Mao JT, Zhu LX, Sharma S, et al. Cocaine inhibits human endothelial cell IL-8 production: the role of transforming growth factor-beta. *Cell Immunol*. 1997;181(1):38–43.
70. Baum MK, Rafie C, Lai S, Sales S, Page B, Campa A. Crack-cocaine use accelerates HIV disease progression in a cohort of HIV-positive drug users. *J Acquir Immune Defic Syndr*. 2009;50(1):93–99.
71. Cook JA, Burke-Miller JK, Cohen MH, et al. Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women. *AIDS*. 2008;22(11):1355–1363.
72. Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Klein RS. A prospective study of HIV disease progression in female and male drug users. *AIDS*. 1999;13(2):257–262.
73. Baldwin GC, Roth MD, Tashkin DP. Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. *J Neuroimmunol*. 1998;83(1–2):133–138.
74. Cearley CN, Blindheim K, Sorg BA, Krueger JM, Churchill L. Acute cocaine increases interleukin-1beta mRNA and immunoreactive cells in the cortex and nucleus accumbens. *Neurochem Res*. 2011;36(4):686–692.
75. Gurwell JA, Nath A, Sun Q, et al. Synergistic neurotoxicity of opioids and human immunodeficiency virus-1 Tat protein in striatal neurons in vitro. *Neuroscience*. 2001;102(3):555–563.
76. Yang Y, Yao H, Lu Y, Wang C, Buch S. Cocaine potentiates astrocyte toxicity mediated by human immunodeficiency virus (HIV-1) protein gp120. *PloS One*. 2010;5(10):e13427.
77. Aksenov MY, Aksenova MV, Nath A, Ray PD, Mactutus CF, Booze RM. Cocaine-mediated enhancement of Tat toxicity in rat hippocampal cell cultures: the role of oxidative stress and D1 dopamine receptor. *Neurotoxicology*. 2006;27(2):217–228.
78. Turchan J, Anderson C, Hauser KF, et al. Estrogen protects against the synergistic toxicity by HIV proteins, methamphetamine and cocaine. *BMC Neurosci*. 2001;2:3.
79. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron*. 2008;57(2):178–201.
80. Dallasta LM, Pisarov LA, Esplen JE, et al. Blood-brain barrier tight junction disruption in human immunodeficiency virus-1 encephalitis. *Am J Pathol*. 1999;155(6):1915–1927.
81. Gandhi N, Saiyed ZM, Napuri J, et al. Interactive role of human immunodeficiency virus type 1 (HIV-1) clade-specific Tat protein and cocaine in blood-brain barrier dysfunction: implications for HIV-1-associated neurocognitive disorder. *J Neurovirol*. 2010;16(4):294–305.
82. Zhang L, Looney D, Taub D, et al. Cocaine opens the blood-brain barrier to HIV-1 invasion. *J Neurovirol*. 1998;4(6):619–626.
83. Dhillon NK, Williams R, Peng F, et al. Cocaine-mediated enhancement of virus replication in macrophages: implications for human immunodeficiency virus-associated dementia. *J Neurovirol*. 2007;13(6):483–495.
84. Fiala M, Eshleman AJ, Cashman J, et al. Cocaine increases human immunodeficiency virus type 1 neuroinvasion through remodeling brain microvascular endothelial cells. *J Neurovirol*. 2005;11(3):281–291.
85. Fiala M, Gan XH, Zhang L, et al. Cocaine enhances monocyte migration across the blood-brain barrier. Cocaine's connection to AIDS dementia and vasculitis? *Adv Exp Med Biol*. 1998;437:199–205.
86. Kanmogne GD, Primeaux C, Grammas P. HIV-1 gp120 proteins alter tight junction protein expression and brain endothelial cell permeability: implications for the pathogenesis of HIV-associated dementia. *J Neuropath Exp Neur*. 2005;64(6):498–505.
87. Yao H, Duan M, Buch S. Cocaine-mediated induction of platelet-derived growth factor: implication for increased vascular permeability. *Blood*. 2011;117(8):2538–2547.
88. Pan W XS, Tu H, Kastin A. Cytokines interact with the blood-brain barrier. In: Dermietzel R, Spray DC, Needergard M, editors. *Blood-Brain Barriers*. *From Ontogeny to Artificial Interfaces*. Weinheim: Wiley; 2006:247–264.
89. Ernst T, Chang L, Oropilla G, Gustavson A, Speck O. Cerebral perfusion abnormalities in abstinent cocaine abusers: a perfusion MRI and SPECT study. *Psychiat Res*. 2000;99(2):63–74.
90. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002;159(10):1642–1652.
91. Griffin WC 3rd, Middaugh LD, Tyor WR. Chronic cocaine exposure in the SCID mouse model of HIV encephalitis. *Brain Res*. 2007;1134(1):214–219.
92. Yao H, Allen JE, Zhu X, Callen S, Buch S. Cocaine and human immunodeficiency virus type 1 gp120 mediate neurotoxicity through overlapping signaling pathways. *J Neurovirol*. 2009;15(2):164–175.

93. Chang L, Wang GJ, Volkow ND, et al. Decreased brain dopamine transporters are related to cognitive deficits in HIV patients with or without cocaine abuse. *NeuroImage*. 2008;42(2):869–878.
94. Meade CS, Lowen SB, MacLean RR, Key MD, Lukas SE. fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. *Psychiat Res*. 2011;192(3): 167–175.
95. Durvasula RS, Myers HF, Satz P, et al. HIV-1, cocaine, and neuropsychological performance in African American men. *J Int Neuropsychol Soc*. 2000;6(3):322–335.
96. Meade CS, Conn NA, Skalski LM, Safren SA. Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. *J Behav Med*. 2011;34(2):128–138.
97. Martin EM, Sullivan TS, Reed RA, et al. Auditory working memory in HIV-1 infection. *J Int Neuropsychol Soc*. 2001;7(1):20–26.
98. Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, Hinkin CH. The effect of recent stimulant use on sustained attention in HIV-infected adults. *J Clin Exp Neuropsychol*. 2006;28(1):29–42.
99. Halkitis PN, Parsons JT, Stirratt MJ. A double epidemic: crystal methamphetamine drug use in relation to HIV transmission among gay men. *J Homosex*. 2001;41(2):17–35.
100. Thiede H, Valleroy LA, MacKellar DA, et al. Regional patterns and correlates of substance use among young men who have sex with men in 7 US urban areas. *Am J Public Health*. 2003;93(11):1915–1921.
101. Purcell DW, Moss S, Remien RH, Woods WJ, Parsons JT. Illicit substance use, sexual risk, and HIV-positive gay and bisexual men: differences by serostatus of casual partners. *AIDS*. 2005;19(Suppl 1):S37–S47.
102. Chan DJ. HIV-1 superinfection: evidence and impact. *Curr HIV Res*. 2004;2(3):271–274.
103. Ellis RJ, Childers ME, Cherner M, Lazzaretto D, Letendre S, Grant I. Increased human immunodeficiency virus loads in active methamphetamine users are explained by reduced effectiveness of antiretroviral therapy. *J Infect Dis*. 2003;188(12):1820–1826.
104. Smith DM, Wong JK, Hightower GK, et al. HIV drug resistance acquired through superinfection. *AIDS*. 2005;19(12):1251–1256.
105. Reiner BC, Keblesh JP, Xiong H. Methamphetamine abuse, HIV infection, and neurotoxicity. *Int J Physiol Pathophysiol Pharmacol*. 2009;1(2):162–179.
106. Liang H, Wang X, Chen H, et al. Methamphetamine enhances HIV infection of macrophages. *Am J Pathol*. 2008;172(6):1617–1624.
107. Gavrilin MA, Mathes LE, Podell M. Methamphetamine enhances cell-associated feline immunodeficiency virus replication in astrocytes. *J Neurovirol*. 2002;8(3):240–249.
108. Yu Q, Zhang D, Walston M, Zhang J, Liu Y, Watson RR. Chronic methamphetamine exposure alters immune function in normal and retrovirus-infected mice. *Int Immunopharmacol*. 2002;2(7):951–962.
109. Theodore S, Cass WA, Maragos WF. Involvement of cytokines in human immunodeficiency virus-1 protein Tat and methamphetamine interactions in the striatum. *Exp Neurol*. 2006;199(2):490–498.
110. Marcondes MC, Flynn C, Watry DD, Zandonatti M, Fox HS. Methamphetamine increases brain viral load and activates natural killer cells in simian immunodeficiency virus-infected monkeys. *Am J Pathol*. 2010;177(1):355–361.
111. Rothrock JF, Rubenstein R, Lyden PD. Ischemic stroke associated with methamphetamine inhalation. *Neurology*. 1988;38(4):589–592.
112. Wang AM, Suojanen JN, Colucci VM, Rumbaugh CL, Hollenberg NK. Cocaine- and methamphetamine-induced acute cerebral vasospasm: an angiographic study in rabbits. *Am J Neuroradiol*. 1990;11(6): 1141–1146.
113. Banerjee A, Zhang X, Manda KR, Banks WA, Ercal N. HIV proteins (gp120 and Tat) and methamphetamine in oxidative stress-induced damage in the brain: potential role of the thiol antioxidant N-acetylcysteine amide. *Free Radic Biol Med*. 2010;48(10):1388–1398.
114. Mahajan SD, Aalinkeel R, Sykes DE, et al. Methamphetamine alters blood brain barrier permeability via the modulation of tight junction expression: implication for HIV-1 neuropathogenesis in the context of drug abuse. *Brain Res*. 2008;1203:133–148.
115. Cass WA, Harned ME, Peters LE, Nath A, Maragos WF. HIV-1 protein Tat potentiation of methamphetamine-induced decreases in evoked overflow of dopamine in the striatum of the rat. *Brain Res*. 2003;984(1–2):133–142.
116. Langford D, Grigorian A, Hurford R, Adame A, Crews L, Masliah E. The role of mitochondrial alterations in the combined toxic effects of human immunodeficiency virus Tat protein and methamphetamine on calbindin positive-neurons. *J Neurovirol*. 2004;10(6): 327–337.
117. Flora G, Lee YW, Nath A, Hennig B, Maragos W, Toborek M. Methamphetamine potentiates HIV-1 Tat protein-mediated activation of redox-sensitive pathways in discrete regions of the brain. *Exp Neurol*. 2003;179(1):60–70.
118. Chana G, Everall IP, Crews L, et al. Cognitive deficits and degeneration of interneurons in HIV+ methamphetamine users. *Neurology*. 2006;67(8):1486–1489.
119. Langford D, Adame A, Grigorian A, et al. Patterns of selective neuronal damage in methamphetamine-user AIDS patients. *J Acquir Immune Defic Syndr*. 2003;34(5):467–474.
120. Qi L, Gang L, Hang KW, et al. Programmed neuronal cell death induced by HIV-1 tat and methamphetamine. *Microsc Res Tech*. 2011. [Epub ahead of print.]
121. Cai NS, Cadet JL. The combination of methamphetamine and of the HIV protein, Tat, induces death of the human neuroblastoma cell line, SH-SY5Y. *Synapse*. 2008;62(7):551–552.
122. Ances BM, Vaida F, Cherner M, et al. HIV and chronic methamphetamine dependence affect cerebral blood flow. *J Neuroimmune Pharmacol*. 2011;6(3):409–419.
123. Chang L, Ernst T, Speck O, Grob CS. Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. *Am J Psychiatry*. 2005;162(2):361–369.
124. Jernigan TL, Gamst AC, Archibald SL, et al. Effects of methamphetamine dependence and HIV infection on cerebral morphology. *Am J Psychirtry*. 2005;162(8):1461–1472.
125. Takaki M, Ujike H, Kodama M, Takehisa Y, Yamamoto A, Kuroda S. Increased expression of synaptophysin and stathmin mRNAs after methamphetamine administration in rat brain. *Neuroreport*. 2001; 12(5):1055–1060.
126. Taylor MJ, Schweinsburg BC, Alhassoon OM, et al. Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. *Journal of Neurovirol*. 2007;13(2):150–159.
127. Rippeth JD, Heaton RK, Carey CL, et al. Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. *J Int Neuropsychol Soc*. 2004;10(1):1–14.
128. Carey CL, Woods SP, Rippeth JD, Gonzalez R, Heaton RK, Grant I. Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. *AIDS Behav*. 2006;10(2):185–190.
129. Sadek JR, Vigil O, Grant I, Heaton RK. The impact of neuropsychological functioning and depressed mood on functional complaints in HIV-1 infection and methamphetamine dependence. *J Clin Exp Neuropsychol*. 2007;29(3):266–276.
130. Galvan FH, Bing EG, Fleishman JA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. *J Stud Alcohol*. 2002;63(2):179–186.
131. Cook RL, Sereika SM, Hunt SC, Woodward WC, Erlen JA, Conigliaro J. Problem drinking and medication adherence among persons with HIV infection. *J Gen Intern Med*. 2001;16(2):83–88.
132. Lefevre F, O'Leary B, Moran M, et al. Alcohol consumption among HIV-infected patients. *J Gen Intern Med*. 1995;10(8):458–460.
133. Petry NM. Alcohol use in HIV patients: what we don't know may hurt us. *Int J STD AIDS*. 1999;10(9):561–570.
134. Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. *J Acquir Immune Defic Syndr*. 2009;52(2):180–202.

135. Zarkin GA, Bray JW, Babor TF, Higgins-Biddle JC. Alcohol drinking patterns and health care utilization in a managed care organization. *Health Serv Res*. 2004;39(3):553–570.
136. Braithwaite RS, Conigliaro J, Roberts MS, et al. Estimating the impact of alcohol consumption on survival for HIV+ individuals. *AIDS Care*. 2007;19(4):459–466.
137. Fisher JC, Bang H, Kapiga SH. The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies. *Sex Transm Dis*. 2007;34(11):856–863.
138. Justus AN, Finn PR, Steinmetz JE. The influence of traits of disinhibition on the association between alcohol use and risky sexual behavior. *Alcohol Clin Exp Res*. 2000;24(7):1028–1035.
139. Persidsky Y, Ho W, Ramirez SH, et al. HIV-1 infection and alcohol abuse: neurocognitive impairment, mechanisms of neurodegeneration and therapeutic interventions. *Brain Behav Immun*. 2011;25(Suppl 1): S61–S70.
140. Dingle GA, Oei TP. Is alcohol a cofactor of HIV and AIDS? Evidence from immunological and behavioral studies. *Psych Bull*. 1997;122(1): 56–71.
141. Meyerhoff DJ. Effects of alcohol and HIV infection on the central nervous system. *Alcohol Res Health*. 2001;25(4):288–298.
142. Tyor WR, Middaugh LD. Do alcohol and cocaine abuse alter the course of HIV-associated dementia complex? *J Leukoc Biol*. 1999;65(4):475–481.
143. Alfonso-Loeches S, Pascual-Lucas M, Blanco AM, Sanchez-Vera I, Guerri C. Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain damage. *J Neurosci*. 2010;30(24):8285–8295.
144. Nelson S, Bagby GJ, Summer WR. Alcohol-induced suppression of tumor necrosis factor – a potential risk factor for secondary infection in the acquired immunodeficiency syndrome. *Prog Clin Biol Res*. 1990;325:211–220.
145. Bagby GJ, Zhang P, Purcell JE, Didier PJ, Nelson S. Chronic binge ethanol consumption accelerates progression of simian immunodeficiency virus disease. *Alcohol Clin Exp Res*. 2006;30(10):1781–1790.
146. Kumar R, Perez-Casanova AE, Tirado G, et al. Increased viral replication in simian immunodeficiency virus/simian-HIV-infected macaques with self-administering model of chronic alcohol consumption. *J Acquir Immune Defic*. 2005;39(4):386–390.
147. Molina PE, Lang CH, McNurlan M, Bagby GJ, Nelson S. Chronic alcohol accentuates simian acquired immunodeficiency syndrome-associated wasting. *Alcohol Clin Exp Res*. 2008;32(1):138–147.
148. Marcondes MC, Watry D, Zandonatti M, Flynn C, Taffe MA, Fox H. Chronic alcohol consumption generates a vulnerable immune environment during early SIV infection in rhesus macaques. *Alcohol Clin Exp Res*. 2008;32(9):1583–1592.
149. Singh AK, Gupta S, Jiang Y. Oxidative stress and protein oxidation in the brain of water drinking and alcohol drinking rats administered the HIV envelope protein, gp120. *J Neurochm*. 2008;104(6): 1478–1493.
150. Acheampong E, Mukhtar M, Parveen Z, et al. Ethanol strongly potentiates apoptosis induced by HIV-1 proteins in primary human brain microvascular endothelial cells. *Virology*. 2002;304(2): 222–234.
151. Haorah J, Knipe B, Leibhart J, Ghorpade A, Persidsky Y. Alcohol-induced oxidative stress in brain endothelial cells causes blood-brain barrier dysfunction. *J Leukoc Biol*. 2005;78(6):1223–1232.
152. Haorah J, Ramirez SH, Schall K, Smith D, Pandya R, Persidsky Y. Oxidative stress activates protein tyrosine kinase and matrix metalloproteinases leading to blood-brain barrier dysfunction. *Journal Neurochm*. 2007;101(2):566–576.
153. Pfefferbaum A, Rosenbloom MJ, Adalsteinsson E, Sullivan EV. Diffusion tensor imaging with quantitative fibre tracking in HIV infection and alcoholism comorbidity: synergistic white matter damage. *Brain*. 2007;130(Pt 1):48–64.
154. Pfefferbaum A, Rosenbloom MJ, Rohlfing T, et al. Contribution of alcoholism to brain dysmorphology in HIV infection: effects on the ventricles and corpus callosum. *Neuroimage*. 2006;33(1):239–251.
155. Bornstein RA, Fama R, Rosenberger P, et al. Drug and alcohol use and neuropsychological performance in asymptomatic HIV infection. *J Neuropsychiatry Clin Neurosci*. 1993;5(3):254–259.
156. Fama R, Rosenbloom MJ, Nichols BN, Pfefferbaum A, Sullivan EV. Working and episodic memory in HIV infection, alcoholism, and their comorbidity: baseline and 1-year follow-up examinations. *Alcohol Clin Exp Res*. 2009;33(10):1815–1824.
157. Rothlind JC, Greenfield TM, Bruce AV, et al. Heavy alcohol consumption in individuals with HIV infection: effects on neuropsychological performance. *J Int Neuropsychol Soc*. 2005;11(1):70–83.
158. Green JE, Saveanu RV, Bornstein RA. The effect of previous alcohol abuse on cognitive function in HIV infection. *Am J Psychiatry*. 2004;161(2):249–254.
159. Schulte T, Mueller-Oehring EM, Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Differential effect of HIV infection and alcoholism on conflict processing, attentional allocation, and perceptual load: evidence from a Stroop Match-to-Sample task. *Biol Psychiatry*. 2005;57(1): 67–75.
160. Sassoon SA, Fama R, Rosenbloom MJ, O'Reilly A, Pfefferbaum A, Sullivan EV. Component cognitive and motor processes of the digit symbol test: differential deficits in alcoholism, HIV infection, and their comorbidity. *Alcohol Clin Exp Res*. 2007;31(8): 1315–1324.
161. Durvasula RS, Myers HF, Mason K, Hinkin C. Relationship between alcohol use/abuse, HIV infection and neuropsychological performance in African American men. *J Clin Exp Neuropsychol*. 2006;28(3): 383–404.
162. Fairfield KM, Eisenberg DM, Davis RB, Libman H, Phillips RS. Patterns of use, expenditures, and perceived efficacy of complementary and alternative therapies in HIV-infected patients. *Arch Intern Med*. 1998;158(20):2257–2264.
163. Sidney S. Marijuana use in HIV-positive and AIDS patients: results of an anonymous mail survey. In: Russo E, editor. *Cannabis Therapeutics in HIV/AIDS*. NewYork, NY: Haworth Integrative Healing Press; 2001:35–41.
164. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515–521.
165. Corless IB, Lindgren T, Holzemer W, et al. Marijuana effectiveness as an HIV self-care strategy. *Clin Nurs Res*. 2009;18(2):172–193.
166. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672–680.
167. Davies SN, Pertwee RG, Riedel G. Functions of cannabinoid receptors in the hippocampus. *Neuropharmacology*. 2002;42(8):993–1007.
168. Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience*. 1997;77(2):299–318.
169. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A*. 1990;87(5):1932–1936.
170. Bolla KI, Eldreth DA, Matochik JA, Cadet JL. Neural substrates of faulty decision-making in abstinent marijuana users. *NeuroImage*. 2005;26(2):480–492.
171. Eldreth DA, Matochik JA, Cadet JL, Bolla KI. Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *NeuroImage*. 2004;23(3):914–920.
172. Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. *Psychopharmacology*. 2006;185(3): 358–368.
173. Friedman H, Klein T, Specter S, et al. Drugs of abuse and virus susceptibility. *Adv Biochem Psychopharmacol*. 1988;44:125–137.
174. Roth MD, Tashkin DP, Whittaker KM, Choi R, Baldwin GC. Tetrahydrocannabinol suppresses immune function and enhances HIV replication in the huPBL-SCID mouse. *Life Sci*. 2005;77(14): 1711–1722.

175. McKallip RJ, Lombard C, Martin BR, Nagarkatti M, Nagarkatti PS. Delta(9)-tetrahydrocannabinol-induced apoptosis in the thymus and spleen as a mechanism of immunosuppression in vitro and in vivo. *J Pharmacol Exp Ther*. 2002;302(2):451–465.
176. Zhu LX, Sharma S, Stolina M, et al. Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. *J Immunol*. 2000;165(1):373–380.
177. Caiaffa WT, Vlahov D, Graham NM, et al. Drug smoking, Pneumocystis carinii pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *Am J Respir Crit Care Med*. 1994;150(6 Pt 1): 1493–1498.
178. Lozada F, Silverman S Jr, Migliorati CA, Conant MA, Volberding PA. Oral manifestations of tumor and opportunistic infections in the acquired immunodeficiency syndrome (AIDS): findings in 53 homosexual men with Kaposi's sarcoma. *Oral Surg Oral Med Oral Pathol*. 1983;56(5):491–494.
179. Newell GR, Mansell PW, Wilson MB, Lynch HK, Spitz MR, Hersh EM. Risk factor analysis among men referred for possible acquired immune deficiency syndrome. *Prev Med*. 1985;14(1):81–91.
180. Rieg G, Lewis RJ, Miller LG, Witt MD, Guerrero M, Daar ES. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. *AIDS Patient Care STDS*. 2008;22(12): 947–954.
181. Whitfield RM, Bechtel LM, Starich GH. The impact of ethanol and Marinol/marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, or dideoxyinosine therapy. *Alcohol Clin Exp Res*. 1997;21(1):122–127.
182. Kuo WH, Wilson TE, Weber KM, et al. Initiation of regular marijuana use among a cohort of women infected with or at risk for HIV in the Women's Interagency HIV Study (WIHS). *AIDS Patient Care STDS*. 2004;18(12):702–713.
183. Operskalski EA, Mack WJ, Strickler HD, et al. Factors associated with hepatitis C viremia in a large cohort of HIV-infected and -uninfected women. *J Clin Virol*. 2008;41(4):255–263.
184. Tindall B, Cooper DA, Donovan B, et al. The Sydney AIDS Project: development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Aust N Z J Med*. 1988;18(1): 8–15.
185. Chao C, Jacobson LP, Jenkins FJ, et al. Recreational drug use and risk of Kaposi's sarcoma in HIV- and HHV-8-coinfected homosexual men. *AIDS Res Hum Retroiruses*. 2009;25(2):149–156.
186. D'Souza G, Palefsky JM, Zhong Y, et al. Marijuana use is not associated with cervical human papillomavirus natural history or cervical neoplasia in HIV-seropositive or HIV-seronegative women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(3):869–872.
187. Wallace JM, Lim R, Browdy BL, et al. Risk factors and outcomes associated with identification of Aspergillus in respiratory specimens from persons with HIV disease. Pulmonary Complications of HIV Infection Study Group. *Chest*. 1998;114(1):131–137.
188. Coates RA, Farewell VT, Raboud J, et al. Cofactors of progression to acquired immunodeficiency syndrome in a cohort of male sexual contacts of men with human immunodeficiency virus disease. *Am J Epidemiol*. 1990;132(4):717–722.
189. Di Franco MJ, Sheppard HW, Hunter DJ, Tosteson TD, Ascher MS. The lack of association of marijuana and other recreational drugs with progression to AIDS in the San Francisco Men's Health Study. *Ann Epidemiol*. 1996;6(4):283–289.
190. Kaslow RA, Blackwelder WC, Ostrow DG, et al. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals. A report from the Multicenter AIDS Cohort Study. *JAMA*. 1989;261(23):3424–3429.
191. Bredt BM, Higuera-Alhino D, Shade SB, Hebert SJ, McCune JM, Abrams DI. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol*. 2002;42(11 Suppl):S82–S89.
192. Chao C, Jacobson LP, Tashkin D, et al. Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men. *Drug Alcohol Dependen*. 2008;94(1–3):165–171.
193. Cabral GA, Griffin-Thomas L. Emerging role of the cannabinoid receptor CB2 in immune regulation: therapeutic prospects for neuroinflammation. *Expert Rev Mol Med*. 2009;11:e3.
194. Cabral GA, Raborn ES, Griffin L, Dennis J, Marciano-Cabral F. CB2 receptors in the brain: role in central immune function. *Br J Pharmacol*. 2008;153(2):240–251.
195. Centonze D, Finazzi-Agro A, Bernardi G, Maccarrone M. The endocannabinoid system in targeting inflammatory neurodegenerative diseases. *Trends Pharmacol Sci*. 2007;28(4):180–187.
196. Molina PE, Winsauer P, Zhang P, et al. Cannabinoid administration attenuates the progression of simian immunodeficiency virus. *AIDS Res Hum Retroviruses*. 2011;27(6):585–592.
197. Crean RD, Tapert SF, Minassian A, Macdonald K, Crane NA, Mason BJ. Effects of Chronic, Heavy Cannabis Use on Executive Functions. *J Addict Med*. 2011;5(1):9–15.
198. Gonzalez R. Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance. *Neuropsychol Rev*. 2007;17(3):347–361.
199. Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology*. 2006;188(4):425–444.
200. Cristiani SA, Pukay-Martin ND, Bornstein RA. Marijuana use and cognitive function in HIV-infected people. *J Neuropsychiatry Clin Neurosci*. 2004;16(3):330–335.
201. Gonzalez R, Schuster RM, Vassileva J, Martin EM. Impact of HIV and a history of marijuana dependence on procedural learning among individuals with a history of substance dependence. *J Clin Exp Neuropsychol*. 2011;33(7):735–752.
202. Chang L, Cloak C, Yakupov R, Ernst T. Combined and independent effects of chronic marijuana use and HIV on brain metabolites. *J Neuroimmune Pharmacol*. 2006;1(1):65–76.
203. Jones R, Dunning J, Nelson M. HIV and hepatitis C co-infection. *Int J Clin Pract*. 2005;59(9):1082–1087.
204. Soriano V, Vispo E, Labarga P, Medrano J, Barreiro P. Viral hepatitis and HIV co-infection. *Antivir Res*. 2010;85(1):303–315.
205. Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study. *HIV Med*. 2004;5(3):174–179.
206. Mohsen AH, Murad S, Easterbrook PJ. Prevalence of hepatitis C in an ethnically diverse HIV-1-infected cohort in south London. *HIV Med*. 2005;6(3):206–215.
207. Verucchi G, Calza L, Manfredi R, Chiodo F. Human immunodeficiency virus and hepatitis C virus coinfection: epidemiology, natural history, therapeutic options and clinical management. *Infection*. 2004;32(1):33–46.
208. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet*. 2000;356(9244):1800–1805.
209. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clin Infect Dis*. 2004;38(1):128–133.
210. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284(4):450–456.
211. Forton DM, Thomas HC, Taylor-Robinson SD. Central nervous system involvement in hepatitis C virus infection. *Metab Brain Dis*. 2004;19(3–4):383–391.
212. Laskus T, Radkowski M, Bednarska A, et al. Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. *J Virol*. 2002;76(19):10064–10068.
213. Bagaglio S, Cinque P, Racca S, et al. Hepatitis C virus populations in the plasma, peripheral blood mononuclear cells and cerebrospinal fluid of HIV/hepatitis C virus-co-infected patients. *AIDS*. 2005; 19(Suppl 3):S151–S165.

214. Fishman SL, Murray JM, Eng FJ, Walewski JL, Morgello S, Branch AD. Molecular and bioinformatic evidence of hepatitis C virus evolution in brain. *J Infect Dis*. 2008;197(4):597–607.
215. Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. *J Virol*. 2004;78(10):5170–5183.
216. Letendre S, Paulino AD, Rockenstein E, et al. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. *J Infect Dis*. 2007;196(3):361–370.
217. Radkowski M, Wilkinson J, Nowicki M, et al. Search for hepatitis C virus negative-strand RNA sequences and analysis of viral sequences in the central nervous system: evidence of replication. *J Virol*. 2002;76(2):600–608.
218. Clifford DB, Yang Y, Evans S. Neurologic consequences of hepatitis C and human immunodeficiency virus coinfection. *J Neurovirol*. 2005;11(Suppl 3):S67–S71.
219. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic complications of HIV disease and their treatment. *Top HIV Med*. 2010;18(2):45–55.
220. Martin-Thormeyer EM, Paul RH. Drug abuse and hepatitis C infection as comorbid features of HIV associated neurocognitive disorder: neurocognitive and neuroimaging features. *Neuropsychol Rev*. 2009; 19(2):215–231.
221. Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. *Curr HIV/AIDS Rep*. 2011;8(1):12–22.
222. Forton DM, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. *Lancet*. 2001;358(9275):38–39.
223. Forton DM, Hamilton G, Allsop JM, et al. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol*. 2008;49(3):316–322.
224. Vivithanaporn P, Maingat F, Lin LT, et al. Hepatitis C virus core protein induces neuroimmune activation and potentiates Human Immunodeficiency Virus-1 neurotoxicity. *PloS one*. 2010;5(9):e12856.
225. Clifford DB, Evans SR, Yang Y, Gulick RM. The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS*. 2005;19(Suppl 3):S64–S71.
226. Forton DM, Allsop JM, Cox IJ, et al. A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection. *AIDS*. 2005;19(Suppl 3):S53–S63.
227. Gonzalez R, Jacobus J, Martin EM. Investigating neurocognitive features of hepatitis C virus infection in drug users: potential challenges and lessons learned from the HIV literature. *Clin Infect Dis*. 2005;41(Suppl 1):S45–S49.
228. Hilsabeck RC, Castellon SA, Hinkin CH. Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clin Infect Dis*. 2005;41(Suppl 1):S38–S44.
229. Cherner M, Suarez P, Casey C, et al. Methamphetamine use parameters do not predict neuropsychological impairment in currently abstinent dependent adults. *Dug Alcohol Depen*. 2010;106(2–3):154–163.
230. Martin EM, Pitrak DL, Weddington W, et al. Cognitive impulsivity and HIV serostatus in substance dependent males. *J Int Neuropsychol Soc*. 2004;10(7):931–938.
231. Thiyagarajan A, Garvey LJ, Pflugrad H, et al. Cerebral function tests reveal differences in HIV-infected subjects with and without chronic HCV co-infection. *Clin Microbiol Infect*. 2010;16(10):1579–1584.
232. von Giesen HJ, Heintges T, Abbasi-Boroudjeni N, et al. Psychomotor slowing in hepatitis C and HIV infection. *J Acquir Immune Defic Syndr*. 2004;35(2):131–137.
233. Cherner M, Letendre S, Heaton RK, et al. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*. 2005;64(8):1343–1347.
234. van Gorp WG, Hinkin CH. Triple trouble: cognitive deficits from hepatitis C, HIV, and methamphetamine. *Neurology*. 2005;64(8):1328–1329.
235. Center for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2009. Department of Health and Human Services, Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/hiv/surveillance/resources/reports/2009report. Accessed Jul 2011.
236. Center for Disease Control and Prevention. HIV Surveillance Report, 2008. Available from: http://www.cdc.gov/hiv/topics/surveillance. Accessed Jul 2011.
237. Gardner ID. The effect of aging on susceptibility to infection. *Rev Infect Dis*. 1980;2(5):801–810.
238. Saltzman RL, Peterson PK. Immunodeficiency of the elderly. *Rev Infect Dis*. 1987;9(6):1127–1139.
239. Veugelers PJ, Strathdee SA, Kaldor JM, et al. Associations of age, immunosuppression, and AIDS among homosexual men in the Tricontinental Seroconverter Study. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;14(5):435–441.
240. Baker JV, Peng G, Rapkin J, et al. Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. *J Acquir Immune Defic Syndr*. 2008;48(5):541–546.
241. Gandhi RT, Spritzler J, Chan E, et al. Effect of baseline- and treatment-related factors on immunologic recovery after initiation of antiretroviral therapy in HIV-1-positive subjects: results from ACTG 384. *J Acuir Immune Defic Syndr*. 2006;42(4):426–434.
242. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis*. 2001;183(8):1290–1294.
243. Valcour V, Shikuma C, Shiramizu B, et al. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. *J Neuroimmunol*. 2004;157(1–2):197–202.
244. Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G. Neurodegeneration and ageing in the HAART era. *J Neuroimmune Pharmacol*. 2009;4(2):163–174.
245. Gelman BB, Schuenke K. Brain aging in acquired immunodeficiency syndrome: increased ubiquitin-protein conjugate is correlated with decreased synaptic protein but not amyloid plaque accumulation. *J Neurovirol*. 2004;10:98–108.
246. Cao W, Jamieson BD, Hultin LE, Hultin PM, Effros RB, Detels R. Premature aging of T cells is associated with faster HIV-1 disease progression. *J Acquir Defic Syndr*. 2009;50(2):137–147.
247. Casau NC. Perspective on HIV infection and aging: emerging research on the horizon. *Clin Infect Dis*. 2005;41(6):855–863.
248. Kilpatrick RD, Rickabaugh T, Hultin LE, et al. Homeostasis of the naive CD4+ T cell compartment during aging. *J Immunol*. 2008; 180(6):1499–1507.
249. Appay V, Fastenackels S, Katlama C, et al. Old age and anti-CMV immunity are associated with altered T-cell reconstitution in HIV-1-infected patients. *AIDS*. 2011;25(15):1813–1822.
250. Rickabaugh TM, Kilpatrick RD, Hultin LE, et al. The dual impact of HIV-1 infection and aging on naive CD4 T-cells: additive and distinct patterns of impairment. *PloS one*. 2011;6(1):e16459.
251. Hoffman RM, Jamieson BD, Bosch RJ, et al. Baseline Immune Phenotypes and CD4+ T Lymphocyte Responses to Antiretroviral Therapy in Younger versus Older HIV-infected Individuals. *J Clin Immunol*. 2011;31(5):873–881.
252. Schacker TW, Bosch RJ, Bennett K, et al. Measurement of naive CD4 cells reliably predicts potential for immune reconstitution in HIV. *J Acquir Immune Defic Syndr*. 2010;54(1):59–62.
253. Ernst T, Chang L. Effect of aging on brain metabolism in antiretroviral-naive HIV patients. *AIDS*. 2004;18(Suppl 1):S61–S67.
254. Chang L, Lee PL, Yiannoutsos CT, et al. A multicenter in vivo proton-MRS study of HIV-associated dementia and its relationship to age. *NeuroImage*. 2004;23(4):1336–1347.
255. Cherner M, Ellis RJ, Lazzaretto D, et al. Effects of HIV-1 infection and aging on neurobehavioral functioning: preliminary findings. *AIDS*. 2004;18(Suppl 1):S27–S34.

256. Valcour V, Paul R, Neuhaus J, Shikuma C. The Effects of Age and HIV on Neuropsychological Performance. *J Int Neuropsychol Soc*. 2011;17(1):190–195.
257. Becker JT, Lopez OL, Dew MA, Aizenstein HJ. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. *AIDS*. 2004;18(Suppl 1):S11–S18.
258. Simone MJ, Appelbaum J. HIV in older adults. *Geriatrics*. 2008; 63(12):6–12.
259. Valcour VG, Shikuma CM, Watters MR, Sacktor NC. Cognitive impairment in older HIV-1-seropositive individuals: prevalence and potential mechanisms. *AIDS*. 2004;18(Suppl 1):S79–S86.
260. Wilkie FL, Goodkin K, Khamis I, et al. Cognitive functioning in younger and older HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2003;33(Suppl 2):S93–S105.
261. Scott JC, Woods SP, Carey CL, Weber E, Bondi MW, Grant I. Neurocognitive Consequences of HIV Infection in Older Adults: An Evaluation of the "Cortical" Hypothesis. *AIDS Behav*. 2011;15(6):1187–1196.
262. Morgan EE, Woods SP, Delano-Wood L, Bondi MW, Grant I. Intraindividual variability in HIV infection: Evidence for greater neurocognitive dispersion in older HIV seropositive adults. *Neuropsychology*. 2011;25(5):645–654.
263. Ettenhofer ML, Hinkin CH, Castellon SA, et al. Aging, neurocognition, and medication adherence in HIV infection. *Am J Geriatrc Psychiatry*. 2009;17(4):281–290.
264. Malaspina L, Woods SP, Moore DJ, et al. Successful cognitive aging in persons living with HIV infection. *J Neurovirol*. 2011;17(1): 110–119.
265. Chilcoat HD, Breslau N. Investigations of causal pathways between PTSD and drug use disorders. *Addict Behav*. 1998;23(6):827–840.
266. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psych*. 2004;61(8):807–816.
267. Letendre SL, Cherner M, Ellis RJ, et al. The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: Biological correlates of disease. *AIDS*. 2005;19(Suppl 3): S72–S78.