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HIV infection Heightens Concurrent Risk of Functional Dependence in Persons With Chronic Methamphetamine Use

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Abstract

Objectives—The causes of disability among chronic methamphetamine (MA) users are multifactorial. The current study examined the additive adverse impact of human immunodeficiency virus (HIV) infection, a common comorbidity in MA users, on functional dependence.

Methods—A large cohort of participants (N=798) stratified by lifetime MA dependence diagnoses (i.e., MA+ or MA–) and HIV serostatus (i.e., HIV+ or HIV–) underwent comprehensive baseline neuromedical, neuropsychiatric, and functional research evaluations, including assessment of neurocognitive symptoms in daily life, instrumental and basic activities of daily living, and employment status.

Results—Independent, additive effects of MA and HIV were observed across all measures of functional dependence, independent of other demographic, psychiatric, and substance use factors. The prevalence of global functional dependence increased in the expected stepwise fashion across the cohort, with the lowest rates in the MA–/HIV– group (29%) and the highest rates in the MA+/HIV+ sample (69%). The impact of HIV on MA-associated functional dependence was moderated by nadir CD4 count, such that MA use was associated with greater disability among those HIV-infected persons with higher, but not lower nadir CD4. Within the MA+/HIV+ cohort, functional dependence was reliably associated with neurocognitive impairment, lower cognitive reserve, polysubstance use, and major depressive disorder.

Conclusions—HIV infection confers an increased concurrent risk of MA-associated disability, particularly among HIV-infected persons without histories of immune compromise. Directed referrals, earlier HIV treatment, and compensatory strategies aimed at counteracting the effects of low cognitive reserve, neurocognitive impairment, and psychiatric comorbidities on functional dependence in MA+/HIV+ individuals may be warranted.

Keywords

Substance use; HIV-associated neurocognitive disorders; Psychiatry; Comorbidity

Introduction

Human immunodeficiency virus (HIV)-related functional dependence is multifactorial in the era of combination antiretroviral therapy (cART), with contributions from a variety of

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commonly encountered demographic (e.g. age; Morgan et al. 2012), medical (e.g., cardiovascular and hepatic disease; Oursler et al. 2011), and neuropsychiatric (e.g., depression; Heaton et al. 2004) cofactors, among which substance use may be particularly impactful. Methamphetamine (MA) dependence is particularly relevant as a major risk factor for HIV infection and a highly prevalent comorbidity (Colfax and Shoptaw 2005). In fact, MA users are more likely to be HIV infected than heroin or opiate users (Gibson et al. 2002), which is primarily driven by injection drug use and risky sexual behaviors. The combination of MA and HIV appears to be more toxic at the neural level than either condition by itself. First, MA increases the expression of HIV cofactors (e.g., CXCR-2) and can increase replication of the virus in astrocytes (e.g., Gavrillin, Mathes, & Podell, 2002). Specifically, MA decreases the function of the blood brain barrier (BBB) by enveloping protein, gp120, which modulates tight junction expression in brain endothelial cells, allowing greater numbers of HIV-infected leukocytes to transport into the brain (e.g., Liang et al., 2008). Additionally, HIV-induced damage of the BBB may also allow for increased concentration of MA within the neural pathways (Kousik, Napier, & Carvey, 2012). Additionally, cross-amplification of the cellular effects of HIV-associated Tat expression by MA additionally shows an increased proinflammatory response leading to greater neurotoxicity among MA+/HIV+ individuals (Flora et al., 2003). The multiple pathways of neurobiological changes result in significant adverse effects for neuronal integrity in this high-risk population; for example, magnetic resonance spectroscopy has demonstrated an association between abnormal cerebral metabolite levels (eg., lower NAA concentrations) and higher HIV plasma viral load in this population, suggesting that MA use may moderate the CNS effects of HIV (Taylor et al., 2007). Subsequently, in combination, MA and HIV place individuals at higher risk for neurocognitive impairment than either condition independently, with specific deficits in learning, memory, motor skills, and attention/working memory (e.g., Rippeth, et al., 2004).

The neural and cognitive effects of MA and HIV infection may be examined in the context of Wilson and Cleary's (1995) model of patient outcomes, which posits a direct pathway between an individual's biological factors to symptom status, both of which lead may help determine functional status. The everyday functioning abilities of an individual with HIV+ and/or MA, therefore, is largely representative of the downstream effects of such neural and cognitive injury, but also may be modulated by a number of concurrent factors (e.g., social and economic support). Not surprisingly, therefore, MA and HIV infection are each independently associated with dependence in everyday functioning outcomes, including unemployment (Weber, 2012a; Heaton et al. 1994), instrumental activities of daily living (IADLs; Henry, Minassian, and Perry 2010; Heaton et al. 2010), and neurobehavioral disturbances (Cattie et al. 2012; Kamat et al. 2012). One everyday outcome for which there is clear evidence regarding an impact of MA within the context of HIV is adherence to cART. Suboptimal adherence to cART (Moore et al. 2012) and reduced optimization of medical care (Craw et al. 2008) contribute to the accelerated HIV disease trajectory and high transmission risk observed among HIV-infected MA users (MA+/HIV+). Despite the established negative impact of MA use on HIV infection at both the neural and behavioral levels, little is known about how these occurrences may impact other critical aspects of everyday functioning (e.g., vocational functioning) in this high-risk population.

Accordingly, the present study evaluates the independent and additive impact of HIV infection on MA-related functional disability. This study extends the existing literature and informs the clinical care of MA users by: 1) including a comprehensive, multi-modal assessment of individual and global functional outcomes; 2) using a large, well-characterized cohort of individuals with and without histories of MA dependence and HIV infection; and 3) identifying the unique demographic, neurocognitive, psychiatric (e.g.,

depression), MA-use, and HIV-related predictors of functional dependence in dually affected individuals.

Methods

Study participants included 798 individuals enrolled from 1999–2012 in National Institutes of Drug Abuse (NIDA)-funded research projects at the University of California, San Diego HIV Neurobehavioral Research Program (HNRP). Participants were stratified by MA dependence diagnoses (i.e., MA – or MA +) and HIV serostatus (i.e., HIV– or HIV+) to yield four study groups: MA–/HIV– (n=217), MA+/HIV– (n=237), MA–/HIV+ (n=155), and MA+/HIV+ (n=189). HIV serostatus was determined by enzyme-linked immunosorbent assays and confirmed by a Western blot test. All participants within the MA+ study groups met DSM-IV-TR criteria for MA dependence in their lifetime and MA abuse or dependence within 18 months of evaluation as measured by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Illness-IV-Text Revision (DSM-IV-TR) (SCID; n=682) or Composite International Diagnostic Interview Version 2.1 (CIDI; n=116). Participants were excluded if they tested positive on a urine toxicology screen for illicit drugs (except marijuana) on the day of testing, met dependence criteria for alcohol or other drugs (except marijuana or prescribed medications) within the past year, had histories of psychotic disorders (e.g., schizophrenia) or severe medical conditions (e.g., seizure disorders, traumatic brain injury), or scored below 70 on the reading subtest of the Wide Range Achievement Test (WRAT; Wilkinson 1993). Participants were not excluded solely on the basis of any prescribed medication. Demographic and HIV disease characteristics are presented in Table 1.

Materials and Procedure

Study procedures were approved by the human subjects institutional review board and all participants provided informed consent.

Everyday Functioning Assessment—The Patient’s Assessment of Own Functioning (PAOFI; Chelune, Heaton, and Lehman 1986), a self-report questionnaire on which participants are asked to rate the frequency with which they have difficulties with memory, language and communication, higher level cognitive and intellectual functioning, motor, sensory-perceptual ability, and recreation, was used to assess each participant’s perceived current level of cognitive functioning in day-to-day life. Participants rate themselves using a 6-point Likert-type scale that ranges from 1 (“almost always”) to 6 (“almost never”). A total score was derived by summing the number of items that were rated 3 or lower (i.e., the problem occurs “fairly often” or more). PAOFI total scores ≥ 3 were classified as impaired (Woods et al. 2004).

The PAOFI also contains an additional single item concerning work functioning, which was used to classify participants as either employed (i.e., full- or part-time; n=290) or unemployed (n=505).

Participants also completed a modified version of the Activities of Daily Living (ADL) Scale (Lawton and Brody 1969), a self-report measure used to assess an individual’s perceived level of independent functioning in various daily activities (Heaton et al. 2004). Participants rate both their current and best (i.e., highest previous) level of functioning on 11 IADLs (i.e., finances, shopping, grocery shopping, understanding reading material/TV, planning social activities, communication, medication management, transportation, cooking, child care, and work) and five basic activities of daily living (BADLs; i.e., housekeeping, home repairs, bathing, dressing, and laundry). For this study, we used the “current” IADL and BADL scores to enhance our sensitivity to MA-related disability given that substance

use disorders commonly emerge prior to the development of functional dependence. Participants were classified as dependent if they reported current difficulties in two or more IADLs or BADLs, respectively (Woods et al. 2004).

For our primary analyses, an overall composite index of functional impairment was derived for each participant by summing the number of impaired functional domains (i.e., everyday cognitive symptoms, employment, IADLs and BADLs; range 0–4). An overall functional composite score of two or greater was used as a cutoff for overall functional dependence (Woods et al. 2004).

Psychiatric assessment—DSM-IV-TR diagnoses of lifetime Major Depressive Disorder (MDD) and non-MA substance use diagnoses (e.g., alcohol) were determined using the SCID or the CIDI 2.1 (Table 1). Detailed MA use characteristics (e.g., frequency and quantity; Table 1) were obtained using a semi-structured timeline follow-back interview (Rippeth et al., 2004).

Neuromedical Evaluation—Each participant had a standardized medical history interview, structured neurological and medical examination, including collection of blood and urine samples consistent with previous studies at the HNRP (Heaton et al. 2011). Trained research staff conducted all medical history interviews and the examinations were performed by clinicians. Medical history questionnaires completed by the participant were used as a guide during the medical interview process to complete case report forms evaluating past medical history, HIV disease stage, antiretroviral history, current medications, and review of systems.

Neuropsychological assessment—Participants were administered a comprehensive neuropsychological (NP) test battery designed to assess domains sensitive to MA dependence (Rippeth et al. 2004) and HIV-associated neurocognitive disorders (HAND; Antinori et al. 2007) including verbal fluency, executive functions, psychomotor speed, attention/working memory, memory, and motor functioning (see Rippeth et al. 2004, for details). Raw scores from individual NP tests were converted to demographically adjusted T-scores, which were converted to domain and global deficit scores (GDS; Carey et al. 2004). GDS values greater than or equal to 0.5 were used to classify global NP Impairment.

Cognitive Reserve—Each participant's years of education and estimated premorbid verbal intelligence (WRAT; Wilkinson 1993) scores were converted to population-based z-scores based on the entire cohort and averaged to derive a putative estimate of premorbid functioning, or cognitive reserve, which was used for analyses, whereby higher values denoted greater levels of estimated cognitive reserve (Morgan et al. 2012b).

Results

A logistic regression was conducted to examine the independent and combined effects of MA and HIV on global functional dependence, while controlling for factors that differed across the study groups (see Table 2). Results indicated significant main effects of both MA and HIV group status, such that MA users were 1.6 times more likely to be functionally dependent ($\chi^2=5.9$, $p=0.02$, [1.1, 2.2]) while HIV infection conferred a 2.5-increased risk for dependence ($\chi^2=29.4$, $p<0.001$, [1.8, 3.5]). Additionally, the interaction between MA and HIV use predicting global functional dependence approached significance ($\chi^2=3.6$, $p=0.058$). As shown in Figure 1, planned pair-wise comparisons showed a stair step effect in which MA–/HIV– individuals had the lowest levels of functional dependence (29% impaired; χ^2 range=33.1–67.2, all $ps<0.001$) and the singly affected groups (MA+/HIV– and MA–/HIV+) did not differ from each other (55 vs. 61% impaired; $\chi^2=1.1$, $p=0.29$). The

MA+/HIV+ individuals experienced the highest level of functional dependence (69% impaired), which differed significantly from the MA-/HIV- ($\chi^2=67.2$, $p<0.001$; OR: 5.6 [3.7, 8.7]) and MA+/HIV- ($\chi^2=8.8$, $p=0.003$; OR: 1.8 [1.2, 2.7]) groups, but only approached significance as compared to MA-/HIV+ individuals ($\chi^2=2.8$, $p=0.09$). This trend-level finding was dissected in a post-hoc analysis to determine the possible influence of HIV disease severity (i.e., history of immunosuppression via nadir CD4 count < 200; Siddique et al. 2006; Munoz-Moreno et al. 2008). We found among individuals with high nadir CD4 counts (i.e., ≥ 200), those who used MA showed significantly greater functional dependence compared to non-MA users ($\chi^2=4.0$, $p=0.04$, OR: 1.7, [1.0, 3.2]). There was no effect of MA among individuals with lower nadir CD4 counts ($\chi^2=1.7$, $p=0.64$). However, once we controlled for those variables that differed between HIV infected MA+ and MA- individuals (i.e., age, education, gender, MA use, and lifetime alcohol, cannabis, and cocaine dependence), we found that, among individuals with high nadir CD4 counts (i.e., ≥ 200), those who had a lifetime history of alcohol dependence showed significantly greater functional dependence ($\chi^2=6.7$, $p=0.002$, OR: 2.8, [1.3, 6.6]) independent of MA use, which did not remain significant. There was no effect of alcohol or MA use among individuals with lower nadir CD4 counts ($ps > 0.05$).

Figure 1 illustrates the rates of domain-specific functional impairments across the groups. Fifty-eight percent of the MA+/HIV+ group was classified as impaired on everyday cognitive symptoms, which was significantly greater than the rate of impairment observed in the MA-/HIV- group ($p<0.05$), though it was comparable to the single risk factor groups ($ps>0.10$). The MA+/HIV+ group had a significantly greater proportion of unemployment relative to each of the remaining groups ($ps<0.01$), and the singly affected groups had higher rates of unemployment compared to MA-/HIV- individuals (χ^2 range=12.5–13.1 $ps<0.001$) but not from each other ($\chi^2=0.25$, $p=0.62$). The MA+/HIV+ group had a greater proportion of individuals classified as IADL dependent relative to the MA-/HIV- comparison group ($ps<0.01$), though rates did not differ from the two single risk factor groups ($ps>0.10$). Additionally, the singly affected groups had greater IADL dependence than MA-/HIV- individuals (χ^2 range= 24.9–34.2, $ps<0.001$) but did not differ from one another ($\chi^2=1.9$, $p=0.17$). In contrast, analyses of BADLs showed only higher rates of dependence in MA-/HIV+ as compared to all other study groups ($ps<0.05$).

A series of logistic regressions were conducted to determine the clinical predictors of global and domain-specific functional impairment within the MA+/HIV+ cohort. With an eye toward parsimony, yet also capitalizing on our large sample, we selected 10 predictor variables *a priori* based on the prior literature to represent essential demographic (i.e., age), MA use (i.e., last MA use and lifetime history of injection MA use), HIV disease (i.e., nadir CD4 count < 200 and currently prescribed antiretroviral (ARV)), neurocognitive (i.e., global neurocognitive impairment and cognitive reserve) and psychiatric (i.e., lifetime histories of MDD, alcohol use disorders, and other non-MA substance use disorders) factors. As shown in Table 3, lower cognitive reserve ($\chi^2=13.8$, $p<0.001$; OR: 2.4, [1.5, 4]), a lifetime history of substance use disorder ($\chi^2=4.9$, $p=0.03$; OR: 2.7, [1.1, 6.6]), and a lifetime history of MDD ($\chi^2=5.0$, $p=0.03$; OR: 2.3, [1.1, 4.9]) each independently predicted global functional impairment among MA+/HIV+ individuals (model: $\chi^2=37.0$, $p<0.001$), while global neurocognitive impairment approached significance ($\chi^2=3.1$, $p=0.08$, OR: 2.0 [0.93, 4.5]). These results were not affected by recency of MA use disorder (i.e., separating out HIV+ individuals with current versus lifetime MA abuse/dependence disorders did not impact global functional dependence; $\chi^2=0.98$, $p=0.32$). When examining each of the functional domains separately, a similar pattern of predictors uniquely predicted IADL impairment [i.e., global neurocognitive impairment ($\chi^2=3.9$, $p=0.05$; OR: 2.0 [1.0, 4.0]), cognitive reserve ($\chi^2=7.1$, $p=0.008$; OR: 1.7 [1.1, 2.7]), other substance use disorder ($\chi^2=4.9$, $p=0.03$; OR: 2.5 [1.1, 5.9]), and MDD ($\chi^2=4.3$, $p=0.04$; OR: 2.0 [1.0, 3.9]); model: $\chi^2=29.2$,

p=0.001]. Similarly, global neurocognitive impairment ($\chi^2=10.4$, p=0.001; OR: 3.1 [1.5, 6.6]) and lower cognitive reserve ($\chi^2=8.7$, p=0.003; OR: 1.9 [0.6, 1.25]) significantly predicted impairment in everyday cognitive symptoms; while MDD approached significance in this model ($\chi^2=3.0$, p=0.09; OR: 1.8 [0.92, 3.6]; model: $\chi^2=32.3$, p<0.001). The model predicting BADL impairment did not reach significance ($\chi^2=14.2$, p=0.16), and unemployment was only significantly predicted by lower cognitive reserve ($\chi^2=11.9$, p<0.001; OR: 2.6 [1.4, 4.9]). Given that education is an important predictor of vocational functioning, in a post-hoc analysis, we separated out education and WRAT performance from our single “cognitive reserve” variable, and found that education ($\chi^2=9.02$, p=0.003; OR: 1.4, [1.1, 1.7]), but not WRAT (p>0.05) uniquely predicted employment status.

Finally, since global neurocognitive impairment was associated with IADL dependence and everyday cognitive symptoms among the MA+/HIV+ individuals, we conducted post-hoc analyses to determine which cognitive domains may be driving these relationships. Poorer performances in executive functions (F(1,187)=4.2, p=0.04), learning (F(1,187)=4.5, p=0.03), and motor (F(1,187)=4.3, p=0.04) abilities were associated with IADL dependence, while worse verbal fluency (F(1,187)=5.7, p=0.02), learning (F(1,187)=5.7, p=0.02), and motor (F(1,187)=10.1, p=0.002) abilities were associated with impairment in everyday cognitive symptoms.

Discussion

The present study examined the degree and nature of multi-modal MA-related functional dependence in the context of HIV infection, revealing a pattern of additivity such that the prevalence of everyday living difficulties was amplified in a stepwise fashion as the number of risk factors increased. Specifically, MA+/HIV+ individuals were most likely to report difficulties, with nearly three-quarters of the cohort evidencing dependence on a broad range of functional capacities, such as employment and instrumental activities (e.g., shopping). When examining each functional domain separately (see Figure 1), we found that the additive pattern of MA use and HIV-infection on functional dependence appeared to be primarily driven by employment status, in which comorbid MA+/HIV+ resulted in 83% unemployment. Employment may be a functional outcome of particular interest not only due to its pragmatic role in individuals' financial sustainability and well being (e.g., contribution to society), but also because of its dynamic nature within HIV and MA use populations. For instance, employment status and vocational capacity are strongly susceptible to HIV- and MA-associated neurocognitive impairment (e.g., learning deficits; van Gorp et al., 2007; Weber et al., 2012a; Heaton et al., 1994) and neuropsychiatric factors commonly comorbid with these risk factors (e.g., depression; Weber et al., 2012a; Heaton et al., 2004). Additionally of note, motivation to work (i.e., HIV-related disability), workplace stigma, as well as drug testing and policies are unique factors that may distinctly influence unemployment status in this high-risk population. Given the significant risk for unemployment, future studies are needed to further delineate the potential contributions of these population-specific variables to vocational functioning among HIV+/MA+ individuals.

Additionally, although the independent effects of HIV infection and MA use were also clearly observed on everyday cognitive symptoms and IADLs, combining these risk factors did not appear to confer an additional probability for dependence on these measures. BADLs, on the other hand, were most clearly impacted by HIV infection, specifically in the absence of MA use, and did not show an effect of MA use. These results extend previous knowledge by examining the contribution of these risk factors both independently and combined across a range of global and individualized measures of everyday functioning (Weber et al. 2012a; Sadek et al. 2007; Heaton et al. 2004). Importantly, these primary findings implicate MA dependence and HIV infection above and beyond relevant cofactors

that affect everyday functioning (e.g., neurocognitive impairment and depression; Wells et al. 1989). These findings have practical implications for treatment providers, particularly when prescribing medications to people with HIV infection, MA use, or both; for instance, all three of these groups may struggle with medication adherence and simply providing prescriptions may not be sufficient to carry through treatment. In fact, even when HIV individuals with everyday functioning difficulties (i.e., IADL dependence, unemployment) implement their own compensatory strategies, they are not able to attain sufficient levels of adherence (Blackstone et al. in press).

Given the trend-level differences between the HIV+/MA+ and HIV+/MA- groups on global functional dependence, we aimed to determine the possible moderating contribution of HIV disease severity (i.e., high vs. low nadir CD4) in this relationship. We found that among HIV+ individuals without a history of severe immunosuppression, MA use significantly predicted functional dependence. However, after controlling for those demographic and substance use variables that differed between the groups, we, in fact, discovered that this finding was driven by lifetime history of alcohol dependence, which conferred a 2.8-fold increased risk of functional dependence independent of MA use. In contrast, this model was not significant among HIV+ individuals with a history of severe immunosuppression (i.e., nadir CD4 < 200). The unique role of alcohol use in this real-world context is commensurate with recent findings from our group in a cohort of acute and early HIV infection (AEH), who also had high nadir CD4 counts (Weber et al., *in press*). In that study, AEH individuals engaging in risky alcohol use were 3.75 times more likely to experience neuropsychiatric distress. The increased neural burden of alcohol use in the context of HIV infection (e.g., greater immune suppression, Wang et al., 2002; neurotoxicity through glutamate imbalance, oxidative damage, and damage to the BBB, Singh et al., 2007a; Singh et al., 2007b) is associated with greater neurocognitive impairment (Schulte et al., 2005; Durvasula et al., 2006; Green et al., 2004) than that found in HIV infection alone. Therefore, we may be observing the downstream functional effects of such molecular and neurocognitive mechanisms associated with such alcohol use among individuals with HIV infection. These findings are also congruent with the reliable associations found between long-term heavy alcohol use and neurocognitive as well as daily functioning impairment in the general population (e.g., Hendrie et al., 1996). In contrast the nonsignificant model among individuals with severe historic immunosuppression may reflect the inability of HIV+ individuals who had been sufficiently ill enough in the past to become disabled and then unable to return to a higher level of function (e.g., return to employment), regardless of substance use. These findings have important implications in the context of the ever-rising CD4 guidelines for initiating cART treatment in that severe immunosuppression may no longer be commonly reached among HIV+ individuals, and instead alcohol use may become a primary disabling factor for these individuals. The current results also complement prior findings showing that alcohol use interferes with effective HIV treatment. Specifically, individuals who are actively using alcohol are more likely to be nonadherent to their cART regimen and experience worse viral load suppression (e.g., Palpeu et al., 2004; Lucas et al., 2002). Taken together, these findings indicate that alcohol use is a risk factor for dysfunction on a range of important daily activities, and may perhaps be an even stronger proxy for functional dependence than MA use among HIV+ individuals.

Given the high prevalence of global functional dependence in the MA+/HIV+ cohort, we sought to further determine the clinical factors driving such high rates of disability in this vulnerable group. Across the higher-level domains (i.e., IADLs, everyday cognitive symptoms, and unemployment), the most robust predictors of functional disability were neurocognitive impairment, lower cognitive reserve, polysubstance use, and major depression. Interestingly, these same risk factors were not associated with basic ADLs, suggesting divergence and specificity of risk factors to higher-level functioning (Vigil et al.

2008; Cahn et al. 1998). Consistent with prior studies, global neurocognitive impairment, and specifically, deficits in memory acquisition and fine-motor speed (Rippeth et al. 2004), were particularly salient predictors of functional impairments among MA+/HIV+ individuals. Psychomotor slowing and deficits in strategic aspects of memory acquisition are prevalent in MA+/HIV+ persons, with the latter being increasingly common (Heaton et al. 2010) and detrimental to adherence (Woods et al. 2010), making them potential targets for neuroremediation. For instance, treatment facilitating encoding of new material and increased psychomotor speed and accuracy such as self-generation of new material (Weber et al. 2012b), spaced retrieval (Neundorfer et al. 2004), or psychomotor training (Baldelli, Boiardi, and Ferrari 2004), may have particularly relevant effects for everyday functioning outcomes in MA+/HIV+. Additionally of note, neither duration of abstinence from MA or recency of MA-related disorder diagnoses were associated with functional outcomes, suggesting that the MA contribution to disability in HIV+ individuals is independent of use timing and therefore may exert its functional impact simply as soon as MA use becomes problematic (i.e., reaches abuse/dependence criterion). As such, prevention of MA use in the context of HIV infection may be particularly critical in order to stave off the significant adverse functional impact of these two conditions.

Relatedly, lower levels of cognitive reserve and education emerged as an important predictors of functional impairment in the MA+/HIV+ group, which has also been implicated as risk factor for syndromic HIV-associated Neurocognitive Disorder (HAND) among neurocognitively impaired HIV+ individuals (Morgan et al 2012b). Cognitive reserve describes the capacity for an individual to counteract the effects of neural injury via enhanced cognitive networks and/or more effective strategy use (Stern 2002). As such, dually affected individuals with lower cognitive reserve may be unable to effectively compensate for the additive neural and cognitive burden of the MA+/HIV+ comorbidity in their daily lives (e.g., an individual lacking the initial capacity to effectively manage medications before being impacted by MA/HIV may be less capable of implementing adherence compensatory strategies once he is impacted). Specifically, however, educational attainment (an important component of cognitive reserve) was found to be the sole driving predictor of employment status among HIV+/MA+ individuals. Education may be a particularly important construct to consider as it may represent the capacity to engage in cognitively demanding activities (e.g., work) as well as an individual's engagement or connection with his community; the latter of which may have important implications for the future development of substance use or risky sexual behaviors (e.g., Rawstorne et al., 2005). Other important characteristics of vocational functioning that were not examined in the current study include history of stable employment (e.g., longest job held), highest job level held (e.g., Hollingshead Index), and job skills. Future studies examining vocational functioning among HIV+/MA+ individuals may benefit by including such potentially moderating variables as community engagement and social support as well as include multiple measures of vocational skills in order to ascertain greater qualitative information regarding the employment characteristics of this high-risk group. Therefore, looking forward, vocational rehabilitation targeted toward HIV+/MA+ individuals with low educational attainment may be particularly fruitful, and encouraging such individuals to return to school for additional educational training and engagement may serve as a protective factor for unemployment in the future.

Results from this study also suggest that MA+/HIV+ individuals with lifetime psychiatric (i.e., major depressive disorder, MDD) and/or substance use disorders (i.e., non-MA and non-alcohol) may be at increased risk for adverse functional outcomes, which is of particular concern given the high prevalence of these non-HIV-related comorbidities in the MA+/HIV+ population (Moore et al. 2012; Urbina and Jones 2004). Consistent with previous research (Morgan et al. 2012a; Sadek et al. 2007; Heaton et al. 2004), lifetime MDD was a

significant, independent predictor of adverse daily functioning, particularly with regard to IADL dependence and everyday cognitive complaints. This is of obvious clinical concern, as mood symptoms may be preventing an individual from functioning at their true ability level (and/or mood symptoms may subsequently be exacerbated by poorer everyday functioning; Sadek et al. 2007). Along similar lines, a lifetime history of polysubstance use was also significantly associated with IADL dependence, suggesting that even relatively remote histories of addiction may carry longer term effects on higher-level aspects of daily functioning. Collectively, these results are consistent with previous research that has found an association between psychiatric and substance use disorders and a number of adverse functional outcomes in HIV infected individuals, including poorer ARV adherence, increased risk behaviors, and lower quality of life (Doyle et al. 2012; Arnsten et al. 2000; Avants et al. 2000). This is of important clinical concern as these common comorbid conditions are remediable (Sherr et al. 2011; Whetten et al. 2006), and early detection and intervention may help to ameliorate functional difficulties for MA+/HIV+ individuals.

Highlighting a few limitations to interpreting the current study findings may guide future research on the deleterious effects of HIV on MA-associated functional disability. First, the primary study outcomes were obtained primarily by self-report, which can be influenced by mood and social desirability factors (Blackstone et al. 2012). Studies integrating multi-modal, objective measures of everyday functioning, such as informant reports, behavioral outcomes (e.g., electronic medication monitoring), and performance-based assessments (e.g., financial management) may be particularly valuable in future studies. Relatedly, the current study did not include a measure of medication adherence as a functional outcome, which may be particularly relevant to this population given the strong positive relationship between ARV adherence and health outcomes among HIV+ individuals as well as the risk for ARV nonadherence in the context of concurrent MA use; future studies are warranted in order to further determine the independent and additive effects of HIV and MA on adherence abilities. Second, the research program from which these data were drawn restricts the generalizability of our findings to chronic MA users, who may differ in important ways from individuals for whom cocaine, opioids, and/or alcohol are their primary substance of choice (e.g., geography, demographics, comorbid conditions). A third limitation of this large cohort study is its cross-sectional nature, which does not allow for inferences to be drawn regarding the timing or trajectory of the additive effects of MA and HIV on daily life. Well-controlled longitudinal investigations are necessary to elucidate the likely dynamic interplay of these two risk factors on disability over the HIV disease course, particularly given the highly variable trajectories of addiction (i.e., relapse-remission cycles) and HAND.

Taken together, it may be helpful to view these data more broadly in the context of Wilson and Cleary's (1995) model of patient outcomes. According to this model, Wilson and Cleary propose a direct relationship between the biological and physiological factors influencing the individual and symptom status, which, together, lead to functional status. Specifically, when an HIV-infected individual becomes intoxicated with MA, a cascade of molecular responses may occur in which increased expression of HIV cofactors, inflammatory response, and infiltration of both HIV and MA into the brain lead to greater neurotoxicity and neural injury, and, subsequently, increased risk for neurocognitive impairment (e.g., executive dysfunction), which, in turn, leads to functional dependence (e.g., unemployment). Importantly, however, there may be several pivotal moderating factors to take into account across these relationships. For instance, although the neural mechanisms of HIV and MA use may be fairly well established, the individual experience of these neural and neurocognitive symptoms may be influenced by characteristics of the individual (e.g., defeatist belief bias due to low mood leading to symptom amplification) or the environment (e.g., lack of social support due to stigma leading to symptom amplification). Additionally,

subsequent functional status may be influenced by individuals' personality or motivation (e.g., decreased dopamine following MA use leading to a state of amotivation or apathy) and/or social and economic supports (e.g., homelessness resulting from chronic MA use). Given the highly complex and potentially variable downstream effects following the neural impact of HIV and MA, it is critical to carefully examine each stage of the disease process both independently and in the context of the larger picture. Future studies are therefore needed to continue to delineate these intricate relationships and examine the other downstream effects of HIV- and MA-related functional dependence, including health perceptions and overall quality of life in order to ascertain the broad spectrum of influence of these highly comorbid risk factors.

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Figure 1.

Prevalence of global and domain-specific functional dependence is greatest among HIV infected individuals with methamphetamine dependence.

Note: HIV+ = HIV seropositive; HIV- = HIV seronegative; MA+ = methamphetamine dependence; MA- = no history of methamphetamine dependence; IADL = Instrumental Activities of Daily Living; BADL = Basic Activities of Daily Living.

Table 1
Demographic, Neuropsychiatric, Methamphetamine (MA) use, and HIV-Disease Characteristics of the study group.

	MA-/HIV- (n=217) (a)	MA+/HIV- (n=237) (b)	MA-/HIV+ (n=155) (c)	MA+/HIV+ (n=189) (d)	p-value
Demographics					
Age	38.5 (12.3)	38.5 (9.0)	41.2 (9.6)	38.4 (7.3)	0.02; c>a,b,d
Gender (% Male)	66	80	88	95	<0.001; a<b,c<d
Ethnicity (% Caucasian)	62	73	64	69	0.058
Education (years)	13.3 (2.3)	11.9 (2.2)	13.2 (2.3)	12.4 (2.4)	<0.001; a,c>b,d
Verbal IQ (WRAT-IV)	101.1 (11.9)	96.3 (10.4)	100.4 (10.1)	98.1 (10.6)	<0.001; b, d<a,c
Cognitive Reserve	0.24 (0.9)	-0.27 (0.7)	0.18 (0.8)	-0.08 (0.9)	<0.001; b<a,c,d; d<a,c
Neuropsychiatric					
Global NP impairment (%)	26	33	35	39	0.048 (pairwise ns)
LT MDD (%)	25	38	52	52	<0.001; a<b<c,d
LT Alcohol dx (%)	29	73	36	63	<0.001; a<c<d<b
Any substance dx (non-MA and non-alcohol; %)	27	71	35	76	<0.001; a<c<b,d
Methamphetamine use					
Age first use (years)	---	21.9 (7.6)	---	23.7 (7.2)	0.02
Last use (days)	---	137.0 (121.7)	---	134.5 (131.8)	0.84
Cumulative duration of use (days) ^I	---	4094.1 (2586.3)	---	2802.1 (2485)	<0.001
IV use ever (%)	---	42	---	49	0.13
Cumulative quantity of use (grams) ^I	---	4926.6 (5307.2)	---	2712.0 (4436.6)	<0.001
HIV disease					
Duration of HIV infection (years)	---	---	8.4 (6.9)	7.6 (6.5)	0.17
Detectable viral load (in plasma: %) (n=327)	---	---	47	55	0.18
Nadir CD4 (<50; %)	---	---	42	43	0.77
Current CD4 ^I	---	---	422 (282, 557)	440 (290, 608)	0.62
On ART (%)	---	---	58	63	0.33
AIDS (%)	---	---	51	45	0.26

^IMedian (inter-quartile range)

Note: WRAT=Wide Range Achievement Test-IV; NP=neuropsychological; LT MDD=lifetime history of Major Depressive Disorder; LT Alcohol dx=lifetime history of alcohol abuse/dependence disorder; Any LT Substance dx (non-MA & non-alcohol)=lifetime history of any substance abuse/dependence disorder other than methamphetamine or alcohol; IV=intravenous; ARV=antiretrovirals; AIDS=acquired immune deficiency syndrome.

Methamphetamine and HIV infection confer independent, additive risks for global functional dependence after controlling for group differences.

Table 2

Variable	Model	Parameter (χ^2)	p-value	Odds Ratio
χ^2	166.6		<0.001	
MA status		5.9	0.02	1.6 [1.09, 2.23]
HIV status		29.4	<0.001	2.5 [1.79, 3.5]
MA*HIV		3.6	0.058	
Age		7.2	0.008	1.02 [1.01, 1.04]
Gender		6.5	0.01	1.8 [1.14, 2.72]
Education		5.5	0.02	3.27 [1.2, 9.09]
Ethnicity (Caucasian vs. others)		0.03	0.87	1.03 [0.73, 1.45]
LT Alcohol dx		0.21	0.65	1.09 [0.75, 1.57]
Any LT substance dx (non-MA and non-alcohol)		12.0	<0.001	1.9 [1.34, 2.84]
LT MDD		20.0	<0.001	2.1 [1.5, 2.9]
Global NP impairment		24.4	<0.001	2.3 [1.7, 3.3]

Note: MA = methamphetamine; MA*HIV = methamphetamine by HIV status interaction; LT Alcohol dx=lifetime history of alcohol abuse/dependence disorder; Any LT Substance dx (non-MA & non-alcohol)=lifetime history of any substance abuse/dependence disorder other than methamphetamine or alcohol; LT MDD = lifetime history of major depressive disorder; Global NP impairment = global neuropsychological impairment.

Table 3
Independent predictors of global functional dependence among MA+/HIV+ individuals.

Variable	Model	Parameter (χ^2)	p-value	Odds Ratio
χ^2	36.7		<0.001	
Age		1.3	0.26	1.03 [0.98, 1.09]
Cognitive reserve		13.8	<0.001	2.4 [1.49, 4.0]
Global NP impairment		3.1	0.08	2.0 [0.93, 4.48]
LT Alcohol dx		0.35	0.55	1.3 [0.57, 2.8]
Any LT substance dx (non-MA and non-alcohol)		4.9	0.03	2.7 [1.12, 6.56]
LT MDD		5.0	0.02	2.3 [1.11, 4.85]
Nadir CD4 (<200)		0.41	0.52	1.3 [0.60, 2.80]
ART status (on/off)		0.46	0.50	1.3 [0.59, 2.92]
Last MA use (days)		0.09	0.76	1.00 [1.00, 1.004]
History of IV MA use		0.22	0.64	1.2 [0.57, 2.52]

Note: Global NP impairment = global neuropsychological impairment; MA = methamphetamine; LT Alcohol dx=lifetime history of alcohol abuse/dependence disorder; Any LT Substance dx (non-MA & non-alcohol)=lifetime history of any substance abuse/dependence disorder other than methamphetamine or alcohol; LT MDD = lifetime history of major depressive disorder.