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Dual-mixed HIV-1 Coreceptor Tropism and HIV-Associated Neurocognitive Deficits

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Abstract

Background—HIV coreceptor usage of CXCR4 (X4) is associated with decreased CD4+ T-cell counts and accelerated disease progression, but the role of X4 tropism in HIV-associated neurocognitive disorders (HAND) has not previously been described.

Methods—This longitudinal study evaluated data on 197 visits from 72 recently HIV-infected persons who had undergone up to 4 sequential neurocognitive assessments over a median of 160 days (IQR 138–192). Phenotypic tropism testing (Trofile ES, Monogram, Biosciences) was performed on stored blood samples. Multivariable mixed model repeated measures regression was used to determine the association between HAND and dual-mixed (DM) viral tropism, estimated duration of infection (EDI), HIV RNA, CD4 count and problematic methamphetamine use.

Results—Six subjects (8.3%) had dual mixed tropism (DM) at their first neurocognitive assessment and four converted to DM in subsequent sampling (for total of 10 DM) at a median EDI of 10.1 months (IQR 7.2–12.2). There were 44 (61.1%) subjects who demonstrated HAND on at least one study visit. HAND was associated with DM tropism (odds ratio 4.4, 95% CI 0.9–20.5) and shorter EDI (odds ratio 1.1 per month earlier, 95% CI 1.0–1.2).

Conclusion—This study found that recency of HIV-1 infection and the development of DM tropism may be associated with HAND in the relatively early stage of infection. Together these data suggest that viral interaction with cellular receptors may play an important role in the early manifestation of HAND.

Keywords

HIV-associated neurocognitive disorders; coreceptor tropism; methamphetamine

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The authors report no conflicts of interest.

Author Contributions

SRM participated in the study design, arranged samples for testing, performed statistical analysis and wrote the primary version of the manuscript; RD performed statistical analysis and participated in writing; SPW was involved in the analysis plan and participated in writing the primary version; EEM was involved in the psychological battery analysis and participated in review of manuscript; DMS participated in study design, enrolled participants, analyzed data and writing of the manuscript, MVV performed the laboratory experiments; SJL and enrolled participants, RKH, SJL, SLL and IG designed the overarching studies that enrolled the subjects and revised the manuscript. All authors read and approved the final manuscript.

Introduction

HIV infection with CXCR4 (X4)-tropic virus versus CCR5 tropic virus (R5) is associated with decreased CD4+ T-cell counts (Chalmet et al., 2012) and accelerated disease progression (Connor, Sheridan, Ceradini, Choe, & Landau, 1997; Daar et al., 2007; Richman & Bozzette, 1994; Shepherd et al., 2008). While the majority of new HIV infections are only R5 tropic (Rieder et al., 2011; Zhu et al., 1993), 12–17% of HIV infected individuals have evidence of viral populations that can use both co-receptors, dual-mixed (DM) within the first year (Chalmet, et al., 2012; de Mendoza et al., 2007; Frange et al., 2009). Eventually, X4 co-receptor usage emerges in approximately half of untreated infected individuals (Berger, Murphy, & Farber, 1999; Sierra et al., 2011). Despite its association with overall disease progression, the role of X4 co-receptor usage has not been studied as a potential risk for HIV-associated neurocognitive disorders (HAND).

Neurocognitive impairment is a common morbidity of HIV and can persist even after HIV replication is suppressed by antiretroviral therapy (Heaton et al., 2010; Letendre, 2011; Letendre, Ances, Gibson, & Ellis, 2007; Valcour, Sithinamsuwan, Letendre, & Ances, 2011). Reasons for the high prevalence of HAND among the chronically infected are not clear, but are generally thought to be influenced by factors related to the host (e.g., age, genetics, and comorbidities including substance abuse) and the virus (e.g., direct and indirect pathways of neuronal injury) (Airolidi et al., 2012; Harezlak et al., 2011). Events in the acute and early phases of HIV infection, which is associated with neuroinflammation, may set the stage for the development of HAND (Lentz et al., 2011; Lentz et al., 2009; Moore et al., 2011). Because CXCR4 tropism is associated with increased generalized immune activation we hypothesized it could also confer increased risk for HAND (Hamlyn et al., 2012). AEH is characterized by neuroinflammatory and immunopathogenic processes that may alter the integrity of neural systems (e.g., Lentz et al., 2011; Lentz et al., 2009; Wang et al., 2011) and neurocognitive functions (e.g., Moore et al., 2011). Prior research shows that between 25 and 60% of persons with AEH evidence HAND (Moore et al., 2011; Weber et al., 2013). The expression of HAND in AEH has been linked to higher HIV RNA in plasma and problematic use of methamphetamine (Weber et al., 2013), which is a risk factor for HIV infection and known to exacerbate the HIV-associated neural injury (e.g., Chang et al., 2007), neurocognitive impairment (e.g. Rippeth et al., 2004), and declines in everyday functioning (Blackstone et al., in press). In this study, we evaluated the associations between viral population tropism and neurocognitive performance in relation to other important factors such as duration of infection, HIV RNA, CD4 counts and histories of problematic methamphetamine use.

Material and Methods

Study Participants and Clinical Data

Study participants were selected from a pool of individuals from the San Diego Primary Infection Cohort (SDPIC) who were co-enrolled in studies within the UCSD HIV Neurobehavioral Research Program and underwent neurocognitive assessments between October 2003 and April 2011. Of the 66 participants with available data on antiretroviral (ART) status at baseline, 60 subjects were naïve, 1 was off treatment, and 5 were currently prescribed ART. All participants had blood samples that could be used for tropism testing (Trofile, Monogram Biosciences) and had undergone at least one neurocognitive assessment. Estimated duration of infection (EDI) was calculated for each participant per established protocols (Fiebig et al., 2003; Hecht et al., 2006; Little et al., 2008), including HIV nucleic acid testing (NAT), HIV antibody testing, detuned enzyme immunoassays (EIA) and Western Blot results (Morris et al., 2010). Samples had been collected at regular clinic visits, aliquoted, frozen, and stored at –80°C. At all timepoints, CD4 cell counts

(LabCorp) and blood plasma and CSF HIV-1 RNA levels (Amplicor HIV-1 Monitor Test, Roche Molecular Systems Inc.) had been quantified. Demographics, clinical data, and standard laboratory values, were also collected in a standardized fashion.

Neurocognitive Test Battery

The neurocognitive test battery was brief, but assessed five cognitive domains of direct relevance to neuroAIDS (Antinori et al., 2007) including measures of executive functions (Trail Making Test B; Reitan & Wolfson, 1993), learning and memory (Hopkins Verbal Learning Test- Revised; HVLT-R Total Trials 1–3 and Delayed Free Recall Trial; Benedict et al., 1998); speed of information processing (Trail Making Test Part A; Reitan & Wolfson, 1993), motor skills (Grooved Pegboard Dominant and Non-dominant hand; Klove, 1963), and semantic verbal fluency (animals; Benton, Hamsher, & Sivan, 1994). Raw scores were converted to T-scores based on demographically-adjusted normative standards (Heaton, et al., 2004; Norman, et al., 2011; Woods, et al., 2005) and follow-up test scores were also corrected for the expected effects of practice (Cysique et al., 2011). T-scores were subsequently transformed into deficit scores ranging from 0 (T-score > 39; no impairment) to 5 (T-score < 20; severe impairment) and were averaged to derive a Global Deficit Score (GDS) (Carey et al., 2004). A standard cut-off score of 0.5 was used to classify individuals with global neurocognitive impairment (Carey, et al., 2004).

Substance Use

Problematic methamphetamine (MA) use was defined as any lifetime diagnosis of abuse or dependence as measured by the Composite International Diagnostic Instrument Second Edition (CIDI 2.0; World Health Organization 1998) ($n = 25$) or scores > 6 on the Drug Abuse Screening Test (DAST; Skinner, 1982) for MA ($n = 45$). Lifetime (LT) histories of alcohol and other (i.e., marijuana, cocaine, hallucinogens, inhalants, opiates, PCP, and sedatives) substance use disorders were also available for the participants who completed the CIDI.

Assessment of Co-receptor Usage

Visits for co-receptor determination were retrospectively selected for blood samples available with viral loads detectable above 1000 HIV RNA copies/ml. Tropism determination was performed using the Monogram Trofile ES assay (Monogram Biosciences inc.) (Wilkin et al., 2011). The latest timepoint was tested, and if tropism was R5 at the last timepoint, then all previous timepoints were assumed to be R5. If a DM or X4 tropism was found at the last timepoint, then a midpoint sample to the baseline visit was identified for tropism testing. Further midpoints were tested sequentially until either DM/X4 was found at the earliest sample or an R5 to DM/X4 shift timepoint was determined, estimated as the midpoint between the R5 and DM/X4 timepoints. In the case of a critical timepoint that on two occasions could not yield a tropism result by Trofile ES (“unreportable”), then a tropism was determined by ultradeep sequencing (UDS) (Wagner et al., 2012).

For UDS, HIV RNA was isolated from blood plasma (QIAamp Viral RNA Mini Kit, Qiagen, Hilden, Germany), cDNA generated (RETROscript® Kit, Applied Biosystems/Ambion, Austin, TX, USA), and UDS (454 GS FLX Titanium, Roche, Branford, CT, USA) of *env*, *gag*, and *pol*. UDS data were examined for coreceptor usage using an online computational prediction tool, geno2pheno 454 (Thielen & Lengauer, 2012), which bases its prediction on the primary sequence of the V3 hypervariable loop of *env*. Results were given as the intrasample percentage of X4 UDS reads below the selected false-positive-rate (FPR) cutoff of 5%.

Statistical Analysis

Baseline characteristics of the sample are reported as N (%), median (interquartile range), or mean (standard deviation). To accommodate within-subject multiple visits and time-varying predictor and outcome variable values, mixed effects logistic regression to predict global neurocognitive impairment (i.e., impaired versus within normal limits) with subject as a random effect was performed in univariable analyses using DM tropism and other candidate predictors: race/ethnicity, age, education, CD4 count, viral load in blood, viral load in CSF (N=38), EDI, and history of problematic MA use (as defined above). A 10% significance level was used to screen out variables considered to have minimal estimating value, and variables remaining were combined into one model with DM tropism, and, one-at-a-time, were removed based on the largest Akaike Information Criterion statistic (AIC) reduction. Interactions between variables were also tested. The final model with the smallest AIC was retained. Odds ratios for impairment and 95% confidence intervals were estimated for prognostic variables in the final model. Each predictor in the final model was then tested separately for association with impairment (T-scores <40) on the individual neurocognitive test scores (practice-adjusted T-scores) using the same mixed effects logistic regression described above for global impairment.

Results

Study cohort characteristics

Study participants (N = 72) were predominantly white (61%) and male (99%) with a median age of 28 years (IQR 23–39 years) (Table 1). The median EDI at the baseline neurocognitive testing was 83 days (IQR 31–118 days). Of the 70 individuals with substance use data available from either the CIDI or the DAST at baseline, 13 (19%) had a lifetime history of problematic MA use. In the subset of participants who had undergone full diagnostic interviews for other substance use disorders (i.e., the CIDI), 67% of the individuals with MA dependence also had lifetime diagnoses of alcohol use disorders (vs. 33% of the persons without MA use disorders) and 78% had histories of other substance use disorders (vs. 10% of the persons without MA use disorders).

There was a total of 197 timepoints assessed with the median number of neurocognitive assessment visits per subject of 3 (IQR 2.3–3, range 1–4), with 8 participants having undergone 1 visit, 10 with 2 visits, 47 with 3 visits, and 7 with 4 visits. The median viral load in plasma at baseline was 4.6 HIV-1 RNA log₁₀ copies/ml (IQR 3.8–5.5 log₁₀ copies/ml), and the median CD4+ T-cell count was 519 cells/ml (IQR 422–705 cells/ml).

Tropism Determination

HIV co-receptor usage determination was done at the earliest available blood sample for all subjects. In some cases this was prior to neurocognitive assessment. There were six (8.3%) individuals demonstrating DM viral populations in blood samples collected at the first (baseline) neurocognitive assessment, and four more who demonstrated DM virus at a later timepoint. Up to four neurocognitive visits were used providing a median time of follow up of 160 days (IQR 138–192). Viral tropism measures were performed with the Trofile ES assay for all timepoints except for two subjects, both of whom had R5 tropic populations determined by geno2pheno testing by ultra deep sequencing. The six subjects with DM at the earliest neurocognitive visit had a median EDI at these dates of 3.3 months (range 2.7–11.2 months). The additional four subjects (for a total of 10 subjects) converted to DM viral populations during follow-up with a median time to conversion of 2.7 months (range 2.5 to 6.9 months).

Tropism and Neurocognitive Impairment

Neurocognitive impairment was observed in 35 individuals (49%) at their first assessment. When examined across all baseline and longitudinal visits, 44 (61%) of study subjects were classified as neurocognitively impaired at some point during the study period. Among the 62 participants who completed longitudinal visits, 33 (53%) had neurocognitive impairment at baseline, 13 (39%) of whom remained neurocognitively impaired at all subsequent visits. Of the 29 longitudinal subjects who did not evidence impairment at baseline, 9 (31%) developed impairment at a subsequent visit. In univariable mixed effects logistic regression analysis, shorter duration of HIV infection (as defined by EDI) was associated with impairment ($p=0.018$). Methamphetamine use, age, education, race/ethnicity, viral load, and CD4 were not significantly associated with neurocognitive impairment (all $p > 0.10$, Table 2). DM tropism, without adjustment for EDI, had an OR of 2.47 (95% CI 0.57–10.69), but was not significant as the sole predictor ($p=0.226$). In the multivariable analysis, the combination of DM tropism and EDI remained in the final model. EDI continued to be significant (OR=1.11 per month shorter duration (95% CI 1.03–1.20, $p=0.007$). Furthermore, after adjusting for EDI, DM tropism showed an increased risk for HAND ($p=0.060$), with an OR of 4.38 (95% CI 0.94–20.48). Results of a series of parallel follow-up analyses examining the associations between EDI, DM tropism, and the individual neurocognitive tests revealed no significant associations between DM or EDI and specific cognitive outcomes (all $ps > 0.10$), suggesting that the battery-based GDS approach to measuring NP may be capturing subtle effects across these individual domains.

Discussion

HAND can emerge early in the course of infection, but we know little about the neurovirological determinants of this important aspect of HIV infection. This study assessed the relationship between HAND and several potential risk factors in 72 individuals with AEH, including HIV-1 coreceptor tropism, EDI, methamphetamine use, and demographics. Results showed that the development of DM co-receptor use reached 13.9% by 12.3 months, which is consistent with cross-sectional estimates of 12–19% in a cohort within the first year of infection (Chalmet, et al., 2012; de Mendoza, et al., 2007; Frange, et al., 2009). Similar to our previous reports (e.g., Weber et al., 2013; Moore et al., 2011), we found HAND to be common in the earliest stages of infection, with (61%) of the sample evidencing neurocognitive impairment at some point during the study period. In univariable analyses, HAND was solely associated with a shorter duration of HIV infection, suggesting that there may be periods of neuroinflammation during the very early stages of infection that are particularly detrimental to neurocognitive functions. Indeed, AEH may be a highly dynamic period, as we observed some evidence of neurocognitive fluctuations over the course of the study; for example, only 39% of subjects with HAND at baseline remained neurocognitively impaired at all subsequent visits, whereas 31% of subjects without HAND at baseline evidenced incident neurocognitive impairment.

DM tropism may play an important role in HAND during AEH, as co-receptor use was associated with a four-fold increased odds of neurocognitive impairment when adjusting for EDI. We cannot precisely determine the causality or mechanisms of the association between DM tropism measured in the blood with HAND. Nevertheless, a variety of candidate mechanisms warrant consideration and may inform future research. For example, DM has been shown to increase immune activation, which could increase risk of neurocognitive impairment (Hamlyn, et al., 2012; Seigny et al., 2004). It is possible that DM affects the central nervous system (CNS) through direct infection of the brain. Although CXCR4 cellular receptors have been found in the CNS it would require the DM virus to be present in the CNS and, so far, most HIV tropism studies in the CNS have reported mainly R5 receptor

usage or DM with affinity for CNS R5 (Fiala et al., 2001; Gray et al., 2009; Lavi, Kolson, Ulrich, Fu, & Gonzalez-Scarano, 1998; Ohagen et al., 2003). The lack of CNS DM virus could be a sampling size issue or a measurement problem of using genetic prediction models that are not sensitive to DM virus (Mefford, Gorry, Kunstman, Wolinsky, & Gabuzda, 2008). In most cases of DM virus in the blood there is concordant tropism in the CNS, but even if there is discordant tropism in these compartments there are still other mechanisms by which DM virus could cause HAND (Spudich et al., 2005).

Several limitations to the interpretation of this study's findings are worth noting. First, this was an observational study using retrospective data with visits that were not uniform in the length of follow up visits and methods used to assess problematic methamphetamine use. A second limitation was the use of a restricted neurocognitive battery, which included only 8 tests. Ideally, future research would include a more comprehensive assessment of neurocognitive functions that, consistent with the Frascati criteria (Antinori et al., 2007), has multiple tests per domain and expands the range of ability areas measured to cover all domains of relevance to neuroAIDS (e.g., attention and working memory, everyday functioning). Finally, our findings are restricted by the relatively small sample of subjects with DM, which may have increased our risk of Type II error for some covariates and/or the individual neurocognitive tests. Nevertheless, the effect size for the association was sufficiently large as to be detectable (and independent) in this preliminary study.

In summary, this study suggests that both early HIV infection and DM tropism play a role in the expression of HAND among ART-naïve persons during the AEH period. Together these data suggest that viral interaction with cellular receptors may play an important role in the early manifestation of HAND. The extent to which DM relates to biomarkers of HAND (e.g., MCP-1) and neuroimaging (e.g., alterations in brain metabolism and/or structure) remains to be determined. Future work is also needed to determine whether the viral tropism shift to DM has persistent effects on HAND following initiation of ART. Successful early treatment of HIV with current ART regimens might thwart phenotypic shifts of viral tropism and possibly reduce burden of HAND.

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Table 1

Study cohort characteristics at the study baseline visit.

Baseline Characteristics	N (%)
Total population	72 (100)
Male, N (%)	71 (99)
Age, Median (IQR)	28 (23–39)
Race/ethnicity, N (%):	
Hispanic	17 (24)
Caucasian	44 (61)
African American	4 (6)
Other	7 (10)
Years of Education, Median (IQR)	15 (13–16)
EDI, Median (IQR)	83 (31–118)
Methamphetamine use (out of 70), N (%)	13 (19)
GDS, Median (IQR)	0.40 (0.13, 0.87)
DM tropism, N (%)	6 (8.3)

IQR=Interquartile Range

EDI=estimated duration of infection (days)

GDS=global deficit score

DM=dual mixed (no pure CXCR4 usage found)

Table 2

Factors Associated with HAND

Estimator of NP impairment	N	No. of visits	Univariable		Multivariable	
			P- value [#]	Odds Ratio (95% CI)	P- value	Odds Ratio (95%CI)
Race/ Ethnicity	72	195	ns			
Age (years)	72	192	ns			
Education (years)	72	192	ns			
CD4 cells/ul ($\times 10^2$ cells)	71	184	ns			
Viral load in CSF (Log ₁₀ copies/ml)	38	64	ns			
Viral load in plasma (Log ₁₀ copies/ml)	71	190	ns			
Estimated duration of HIV infection [*]	72	195	0.018	1.09 (1.01, 1.17)	0.007	1.11 (1.03, 1.20)
Tropism ^{**}	72	195	0.226	2.47 (0.57, 10.69)	0.060	4.38 (0.94, 20.48)
Methamphetamine ^{***}	70	191	ns			

[#] ns=not significant (p>0.10);

^{*} High-risk category for odds ratio is 1 month shorter;

^{**} High-risk category for odds ratio is DM;

^{***} lifetime history of problematic methamphetamine use