Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort

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Objective: Differences in antiretroviral distribution into the central nervous system (CNS) may impact neurocognitive status. We assessed the relationship between estimates of antiretroviral therapy penetration into the CNS, using a published ranking system, and neurocognitive status in HIV-positive participants with plasma HIV-1 RNA (vRNA) suppression.

Design: Participants with at least 6 weeks ongoing antiretroviral drug use and vRNA less than 50 copies/ml ($N = 2636$; 83% male, median baseline CD4 T cells: 244 cells/μl) had at least one neuroscreen assessment [Trail Making Test, Part A and B; Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol] at 10 413 neurovisits. Neuroscreen test scores were demographically adjusted and converted to *Z*-scores (NPZ3: lower scores imply more impairment). Central nervous system penetration effectiveness (CPE) ranks of 0.0 (low), 0.5 (medium), or 1.0 (high) were assigned to antiretrovirals and summed per regimen, per neurovisit.

Methods: Multivariate linear regression models using generalized estimating equations assessed NPZ3 scores with respect to antiretroviral regimen. Covariates were retained if $P \leq 0.1$.

Results: A final model demonstrated that better NPZ3 scores were associated with higher CPE among participants taking more than three antiretroviral drugs (+0.07 per one unit increase in CPE score; $P = 0.004$) but not among participants with three or less antiretroviral drugs in the regimen (+0.01; $P = 0.5$). Results were adjusted for demographics, injection drug use, hepatitis C virus serostatus, CD4 cell count (current and nadir), baseline vRNA, antiretroviral experience, and years since first antiretroviral drug use.

Conclusion: Use of antiretroviral drugs with better estimated CNS penetration may be associated with better neurocognitive functioning; some people may require more than three antiretroviral drugs to treat HIV in the CNS. Clinically this means antiretroviral regimens could be designed to optimize estimated CNS penetration without sacrificing virologic and immunologic benefits.

AIDS 2011, **25**:000–000

Keywords: antiretroviral agents, central nervous system, HIV, HIV-1 RNA suppression, neurologic impairment

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Received: 26 July 2010; revised: 27 September 2010; accepted: 8 October 2010.

DOI:10.1097/QAD.0b013e32834171f8

Introduction

HIV enters the central nervous system (CNS) within days of initial infection and is present within the CNS throughout the course of disease, frequently leading to HIV-associated neurocognitive disorders (HAND) [1]. Treatment with antiretroviral drugs can result in significant neurocognitive improvement in many individuals with HAND [2]. Nevertheless, improvement with antiretroviral treatment (ART) varies greatly between individuals [3], and several cohort studies have demonstrated that HAND can persist despite virologic suppression and immune recovery on ART [4,5]. One hypothesized explanation for persisting HAND is inadequate treatment of CNS HIV infection due to relatively poor penetration of many antiretrovirals across the blood–brain barrier [6]. With limited CNS penetration, it is possible that subtherapeutic levels of antiretroviral drugs could lead to the development of resistant virus in the nervous system and might not reverse neurologic deficits as well as antiretroviral drugs with better CNS penetration [7,8]. To draw conclusions regarding the significance of drug penetration into the CNS, it is important to examine persons who have plasma HIV-1 RNA (vRNA) viral suppression. In this group there is an opportunity to assess whether antiretroviral regimens that lead to vRNA suppression have differing effects on neurocognitive impairment.

In this analysis, we use data from the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort. Participants from this prospective study provide a unique opportunity to assess estimated CNS penetration and neurocognitive function; the study consists of a large sample of participants randomized to a wide variety of antiretroviral regimens in ACTG clinical trials, who completed neurocognitive assessments at predetermined visits.

Methods

Study population

Participants in the ALLRT cohort study enrolled from 26 United States-based ACTG clinical trials [9]. In the parent clinical trials, participants were prospectively randomized to receive ART, to immune-based therapies, or to participate in a new treatment strategy; participants were either antiretroviral-naive or antiretroviral-experienced when entering their parent clinical trial (baseline). Long-term observational follow-up continued based on the ALLRT protocol during and after the participants completed their parent clinical trial. ALLRT visits were every 16 weeks. Participants from two treatment interruption studies and two studies in which antiretroviral medications are still blinded were not eligible for this analysis. Enrollment into parent clinical trials began in 1997, and analysis was performed on data collected through June 30, 2008. Institutional Review Boards at ACTG sites approved the ALLRT protocol; all participants provided signed written informed consent.

Data collection

Demographics (sex, race/ethnicity, age) and injection drug use status were collected once at baseline; years of education were collected when the first neuroscreen assessment was completed. Hepatitis C antibody testing was performed at baseline or ALLRT entry (requirements for parent clinical trials varied); subjects were re-screened on ALLRT every 96 weeks. $CD4^+$ T-cell count and HIV-1 RNA plasma viral load were measured at 16-week visits using routine clinical laboratory methods.

Neuroscreen assessments and antiretroviral regimens

Neuroscreen assessments were conducted by trained and certified personnel every 48 weeks in ALLRT and consisted of three tests: Trail Making Test, Part A and B (Trail A, B) [10], and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Test [11]. Trail making test scores were reported as the time it took to complete the test, whereas the score for the WAIS-R test was reported as the number of symbols correctly completed within 90 s. These examinations were designed to be uncomplicated; trained non-neuropsychologist personnel can reliably administer them in 10–15 min. A web-based tool, developed to facilitate training and certification, included forms, instructions for their use, as well as training videos for the Trail A, B and WAIS-R. Certification to administer the neuropsychologic examinations was granted when study site personnel completed an online test. A published validation study [12] assessed the relationship between neurologic screening test performance and clinical diagnoses as classified according to modern nomenclature [1], supporting our ability to interpret the screening data as it relates to clinical diagnoses.

Raw scores from Trail Making Test A, B were standardized, adjusting for sex, age, educational status, and black vs. nonblack race, whereas Digit Symbol Scores were prorated to WAIS-III scaled scores and standardized adjusting for sex, age, educational status, and race/ethnicity (white, black and Hispanic) [13,14]. Standardized scores (*T*-scores) have a normal distribution with a mean of 50 and standard deviation of 10. *T*-scores were converted to *Z*-scores ($Z\text{-score} = (T\text{-score} - 50)/10$), which were used to create a composite neuropsychologic score (NPZ3 score) that was the average of the three individual *Z*-scores; participants with lower scores are more neurologically impaired than participants with higher scores. Participants who did not take Trail A, B and WAIS-R tests due to HIV-associated neurologic disease were assigned a corresponding *Z*-score of -2 ($n = 11$). In the event more than one neuroscreen assessment was

conducted within a 48-week interval, the evaluation closest to the center of the interval was used.

For each visit an antiretroviral regimen was determined. Start and stop dates of all antiretroviral drugs taken by a participant were self-reported and recorded at each 16-week study visit; treatment interruptions of less than 21 days, per the ALLRT protocol, were not documented. A participant's current antiretroviral regimen, associated with an NPZ3 score, was defined as the antiretroviral regimen taken consistently for at least 6 weeks before and through the date the neuroscreen assessment was completed. Neurologic visits were excluded from analysis if a participant was off antiretroviral drugs for more than 21 days or switched their antiretroviral regimen during the 6 weeks before the visit. All visits included in the analysis for previously antiretroviral-naive participants are postbaseline, because none of these participants had 6 weeks of antiretroviral therapy at the time they entered their parent clinical trial. Participant could switch from one regimen to another over the course of a study (i.e., be taking a three-drug regimen and then switch to a four-drug regimen); we used analysis techniques for repeated measures to account for changes among participants, over time.

Antiretroviral central nervous system penetration effectiveness ranking system

The method for ranking the antiviral effectiveness of antiretroviral drugs in the CNS has been previously described [15–18]. Briefly, this hierarchical and adaptive approach to ranking the effectiveness of antiretrovirals in the protected CNS environment uses physicochemical, pharmacokinetic, and pharmacodynamic data to categorically rank the antiretrovirals. Physicochemical characteristics considered in constructing the rank included molecular weight, lipophilicity (octanol–water partition coefficients), charge at physiologic pH (dissociation constants), and protein binding. Pharmacokinetic data are considered more influential than physicochemical characteristics and compare drug concentrations in the CNS [typically cerebrospinal fluid (CSF)] to drug concentrations in blood and inhibitory concentrations for wild-type HIV-1. Pharmacodynamic data are considered the most important, but few drugs have usable pharmacodynamic data because the criteria for data consideration require the administration of the antiretroviral in a manner that allows determination of its independent effect on nervous system-relevant outcomes. These data were compiled and compared between drugs, which were then categorized into one of three categories: 0.0 (low: relatively poor estimated CNS penetration), 0.5 (medium: intermediate estimated CNS penetration), or 1.0 (high: relatively good estimated CNS penetration). The ranks are summarized in Table 1. In this approach, ritonavir used in subtherapeutic 'boosting' doses is not counted as an individual drug; instead, different ranks are used for 'boosted' and 'unboosted' protease inhibitors. Estimated antiretroviral CNS penetration at each neurologic visit was calculated as the sum of the individual central nervous system penetration effectiveness (CPE) ranks for each drug contained in the current antiretroviral regimen, resulting in one CPE rank per antiretroviral regimen, per neuroscreen assessment. Using this ranking system, higher CPE ranks identify regimens that have greater estimated distribution into, and therefore effectiveness in, the CNS.

Data analysis

Of the 3302 ALLRT participants eligible for analysis, 3245 participants (98%) had at least one neuroscreen assessment (Fig. 1). Demographic information necessary for adjusting NPZ3 scores was incomplete for 90

Table 1. Antiretroviral central nervous system penetration scoring system: central nervous system penetration effectiveness score.

	CPE Score		
Drug class	1	0.5	0
Nucleoside reverse transcriptase inhibitor	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine	Adefovir Zalcitabine Didanosine Tenofovir
Non-nucleoside reverse transcriptase inhibitor	Delavirdine Nevirapine	Efavirenz	
Protease inhibitor[a]	Amprenavir-r Darunavir Fosamprenavir-r Lopinavir-r Indinavir-r	Amprenavir Atazanavir Atazanavir-r Fosamprenavir Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Integrase inhibitors		Elvitegravir Raltegravir	
Entry inhibitors	Vicriviroc Maraviroc		Enfuvirtide T-1249

CPE, CNS penetration effectiveness.
[a]Amprenavir-r, ritonavir-boosted amprenavir; Fosamprenavir-r, ritonavir-boosted fosamprenavir; Lopinavir-r, ritonavir-boosted lpinavir; Indinavir-r, ritonavir-boosted indinavir; Atazanavir-r, ritonavir-boosted atazanavir; Saquinavir-r, ritonavir-boosted saquinavir; Tipranavir-r, ritonavir-boosted tipranavir.

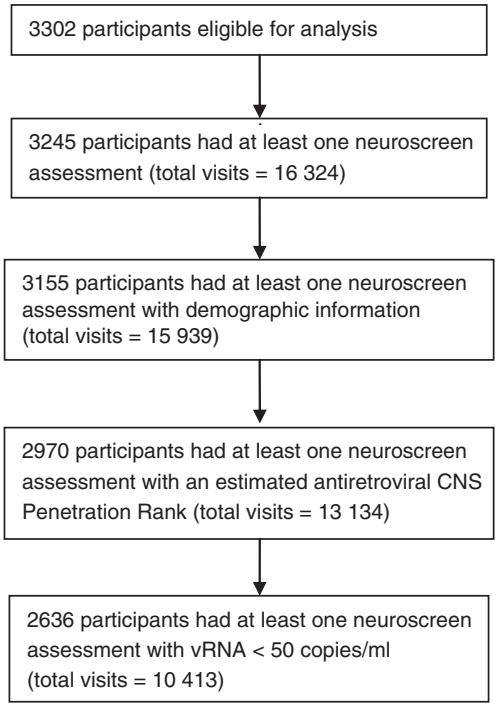

Fig. 1. Flow diagram for participants in the analysis. CNS, central nervous system.

participants. For 17% of the neurologic visits, available antiretroviral data did not meet criteria required to assess the CNS penetration rank (11%: participants were off antiretroviral drugs for the entire 6 weeks before the visit; 4%: participants were off antiretroviral drugs for more than 21 days, but less than 6 weeks, before the visit; 2%: participants switched antiretroviral regimens). A total of 2970 participants had at least one NPZ3 score with an estimated CPE rank (total visits: 13 134). In this analysis, only participants with a vRNA less than 50 copies/ml at the time of a neuroscreen assessment were included. In total, 2636 participants had 10 413 visits with a neuroscreen assessment at which plasma vRNA was less than 50 copies/ml; these visits are the time points included in this analysis.

Linear regression models, using generalized estimating equations (GEEs) to account for repeated measures, were fit to assess the relationship between estimates of ART penetration in the CNS (CPE ranks) and neurocognitive outcomes (NPZ3). Univariate regressions were used to examine unadjusted relationships between covariates and NPZ3 scores. Covariates included baseline demographics, injection drug use, and baseline and time-updated concurrent $CD4^+$ T-cell count, antiretroviral status at parent entry, years since first antiretroviral drug use, and total number of antiretroviral drugs in the current regimen. Multiple linear regression models, constructed using backward elimination, were used to assess the relationship between the CPE rank and NPZ3 score, while adjusting for potential confounders; potential confounders were retained if the *P*-value was 0.1 or less. We assessed collinearity; none was identified.

Additional evaluation of intermediate models was conducted. Examination of the addition of one potential confounder at a time to the simple CPE rank and NPZ score model and construction of the final multivariate model using forward selection were used to initially identify covariates that altered the CPE effect estimate. Number of antiretroviral drugs was a key covariate that, when added to the model, caused a change in the CPE score estimate; further exploration showed evidence of an interaction. The cut-point for the number of antiretroviral drugs was based on changes in the point estimates when the interaction was examined in modeling. The final, adjusted model includes the interaction between CPE score and number of antiretroviral drugs; the two main effects reflect every one score increase in the CPE among observations wherein there are less than or equal to three antiretrovirals in the regimen and there are four or more antiretrovirals in the regimen. Results from the model are estimates of the change in NPZ3 score, per unit of each covariate. Data were analyzed using SAS version 9.13 (SAS Institute Inc, Cary, North Carolina, USA).

Results

Of the 2636 ALLRT participants analyzed, the majority were male (83%), white, non-Hispanic (53%) with a baseline median age of 40 and 14 years of education; only 8% reported past or current injection drug use (Table 2). Nadir $CD4^+$ T-cell counts were lower than the CD4 cell counts at baseline (median: 182 vs. 244 cells/μl). Participants had a median follow-up time of 4.7 years, which was defined as time from parent clinical trial entry (baseline) to last neuroscreen assessment; median number of NPZ3 scores per participants was 4. The relationship between CD4 T-cell count and CPE was examined; there was no correlation between a participant's CD4 cell count and their CPE rank (Spearman correlation coefficient: first neurologic visit, −0.05; second neurologic visit, −0.04).

The overall median CPE rank score was 2.0 (first quartile, third quartile): (1.5, 2.5; 73%, ≤2.0) (Table 3). Median CPE rank score was 1.5 (1.0, 2.0) among observations in which there were three antiretrovirals or less in the regimen and was 2.5 (2.0, 3.0) when there were more than three antiretrovirals in the regimen. None of the participants taking three antiretrovirals or less had a CPE score higher than 2.5, whereas 43% of the observations among participants taking more than three antiretroviral drugs had CPE scores of 3 or higher. The majority of observations (63%) were among participants who were on three antiretroviral medications when the CPE rank was calculated; approximately 30% were on four antiretrovirals, and less than 8% were on fewer than three

Table 2. Baseline demographics, behavioral, clinical, virologic, and neurologic data ($N = 2636$).

Characteristic	Total
Sex	
Male	2195 (83%)
Female	441 (17%)
Race	
White non-Hispanic	1384 (53%)
Black non-Hispanic	730 (28%)
Hispanic (regardless of race)	522 (20%)
Age (years)	
Median (Q1, Q3)	40 (34, 47)
CD4 cell count (cells/μl) at baseline	
Median	243.5
0–50	435 (17%)
51–200	670 (25%)
>200	1529 (58%)
Missing	2 (0%)
Nadir CD4 (cells/μl) on or before baseline	
Median	182
0–50	589 (22%)
51–200	834 (32%)
>200	1213 (46%)
Viral load (copies/ml) at baseline	
Median	43 036
0–10 000	685 (26%)
>10 000–100 000	1035 (39%)
>100 000	916 (35%)
Injection drug use at baseline	
None	2415 (92%)
Reported (currently or previously)	221 (8%)
Hepatitis C Ab status	
Negative	2228 (85%)
Positive ever	278 (11%)
Years of education	
Median (Q1, Q3)	14 (12, 16)
Number of neurology visits	
Median (Q1, Q3)	4 (2, 6)
Years from baseline to the first neurology visit	
Median (Q1, Q3)	1.4 (0.9, 2.6)
Years from baseline to the last neurology visit	
Median (Q1, Q3)	4.7 (3.0, 7.5)
Antiretroviral-status baseline	
Naive	69%
Years from first neurovisit to last neurovisit	
Median (Q1, Q3)	3.1 (1.0, 5.5)

Table 3. Distribution of the central nervous system penetration effectiveness score by number of antiretrovirals in the regimen (total visits = 10 413).

	Number of ARVs in regimen		
CPE score	Overall ($N = 10\,413$)	ARVs ≤ 3 ($N = 7367$)	ARVs > 3 ($N = 3046$)
0–0.5	323 (3%)	319 (4%)	4 (<1%)
1	1862 (18%)	1629 (22%)	233 (8%)
1.5	2048 (20%)	1787 (24%)	261 (9%)
2	3412 (33%)	2753 (37%)	659 (22%)
2.5	1458 (14%)	864 (12%)	594 (20%)
3	1052 (10%)	15 (0%)	1037 (34%)
3.5	241 (2%)	0 (0%)	241 (8%)
4–4.5	17 (<1%)	0 (0%)	17 (1%)
Median	2	1.5	2.5
Q1, Q3	1.5, 2.5	1, 2	2, 3

ARV, antiretroviral; CPE, central nervous system penetration effectiveness.

antiretrovirals (median: three antiretrovirals; Q1, Q3: 3, 4). Fifty-one percent of participants were on the same antiretroviral regimen throughout the analysis period and hence had the same CPE rank; 36% had only one change in their antiretroviral regimen. A majority (61%; $n = 1618$) had the same CPE rank at each neuroscreen measurement; fewer than 5% of our study population had more than two different CPE ranks. A higher percentage of participants with four antiretrovirals had a protease inhibitor in their regimen as compared to participants with three antiretrovirals in the regimen (59% vs. 38%). There was little variation in median NPZ3 scores by CPE rank, when evaluating this relationship at the first neurovisit; median time to the first neuroscreen assessment was 1.4 years from baseline. Additionally, the mean (−0.3) and median (−0.3) NPZ3 scores were the same among observations in which there were three or four antiretroviral drugs in the regimen.

In univariate regression analyses, there was no association between CPE rank and NPZ3 scores [estimate of the change in NPZ3 score per one unit in CPE score: −0.0049, 95% confidence interval (95% CI −0.0318, 0.0219), $P = 0.7$]. However, there was effect measure modification between the CPE score and the total number of antiretroviral drugs in the regimen. An association was seen in the observations in which there were more than three antiretrovirals in the regimen [estimate: 0.07, 95% CI (0.02, 0.11), $P = 0.005$] but not where there were three antiretrovirals or less in the regimen [estimate: −0.02, 95% CI (−0.05, 0.02), $P = 0.3$]. Injection drug use [estimate: −0.12, $P = 0.03$] and a positive hepatitis C virus (HCV) serostatus [estimate: −0.18, $P < 0.001$] were independently associated with worse performance on the neuroscreen assessment, whereas a nadir CD4 cell count above 200 (vs. ≤200) was associated with better performance. All baseline demographic characteristics were associated with changes in the NPZ3 score ($P < 0.05$) (Table 4).

In the final multivariate linear regression model, when adjusting for potential confounders in which $P \leq 0.1$, results demonstrated that for every one unit increase in the CPE rank there was an associated increase in the NPZ3 score among participants with more than three antiretroviral drugs in the regimen [estimate: 0.07, 95% CI (0.02, 0.12), $P = 0.004$] but not among participants taking three antiretrovirals or less [estimate: 0.01, 95% CI (−0.02, 0.05), $P = 0.5$] (Table 4). Thus, a participant with a CPE rank of 4.0 who was taking more than three antiretroviral drugs could have an NPZ3 score of 0.20, whereas a participant with identical covariate characteristics with a CPE rank of 1.0 would have an NPZ3 score of −0.01. Longer duration since initiating antiretroviral drug use was associated with better performance on neurocognitive assessments [estimate per 1 year increase since first antiretroviral use: 0.05; 95% CI 0.04, 0.06], as were nadir CD4 cell counts above 200 [estimate 0.06;

Table 4. Univariate and multivariate linear regression estimates of the change in NPZ3 score and 95% confidence intervals for the association between central nervous system penetration effectiveness score, immunologic, virologic, additional risk factors, and neurologic function (NPZ3 score), in which plasma HIV RNA <50 (copies/ml) at the neurovisit ($N = 2636$).

Main variable	Univariate[a,b] Change in NPZ3 score (95% CI)	*P*	Multivariate[a,b] Change in NPZ3 score (95% CI)	*P*
CPE score				
Every 1 score increase	−0.01 (−0.03,0.02)	0.7		
CPE score (every 1 score increase)				
Among observation with ≤3 ARVs	−0.02 (−0.05,0.02)	0.3	0.01 (−0.02,0.05)	0.5
Among observation with >3 ARVs	0.07 (0.02,0.11)	0.005	0.07 (0.02,0.12)	0.004
Confounders				
Sex				
Female vs. male	−0.13 (−0.21,−0.05)	0.002	−0.13 (−0.22,−0.05)	0.001
Race/ethnicity				
White vs. black	−0.11 (−0.18,−0.04)	0.002	−0.18 (−0.25,−0.1)	<0.001
Hispanic vs. black	−0.48 (−0.56,−0.4)	<0.001	−0.48 (−0.57,−0.4)	<0.001
Age				
Every 10 year increase in age	−0.07 (−0.1,−0.03)	<0.001	−0.09 (−0.12,−0.05)	<0.001
Years of education				
Every 1 year increase	0.03 (0.02,0.04)	<0.001	0.02 (0.01,0.03)	<0.001
Injection drug use				
Reported vs. not reported	−0.12 (−0.22,−0.01)	0.03		
HCV serostatus				
Ever positive vs. never or unknown	−0.18 (−0.28,−0.09)	<0.001	−0.15 (−0.24,−0.06)	0.001
Baseline nadir CD4 cell count (cells/μl)				
>200 vs. ≤200	0.09 (0.03,0.15)	0.003	0.06 (−0.01,0.13)	0.08
Baseline CD4 cell count (cells/μl)				
>200 vs. ≤200	0.09 (0.03,0.16)	0.003		
Current CD4 cell count (cells/μl)				
351–500 vs. ≤350	0.07 (0.03,0.11)	<0.001	0.03 (−0.01,0.06)	0.1
>500 vs. ≤350	0.1 (0.06,0.14)	<0.001	0.04 (−0.01,0.08)	0.09
Baseline plasma HIV RNA (copies/ml)				
10 000–100 000 vs. <10 000	−0.06 (−0.13,0.02)	0.1	−0.1 (−0.19,−0.01)	0.02
>100 000 vs. <10 000	−0.06 (−0.14,0.02)	0.1	−0.09 (−0.19,0.01)	0.08
Baseline ARV status				
ARV experienced vs. ARV naive	−0.02 (−0.09,0.04)	0.5	−0.38 (−0.48,−0.29)	<0.001
Years since first ARV use				
Every 1 year increase	0.03 (0.03,0.04)	<0.001	0.05 (0.04,0.06)	<0.001

ARV, antiretroviral; CPE, central nervous system penetration effectiveness, HCV, hepatitis C virus.
[a]Number of antiretroviral drugs in the regimen (>3 vs. ≤3); estimate: −0.23 (univariate), −0.16 (multivariate). These variables cannot be interpreted alone but are in the model because of the interaction.
[b]Interaction term [#ARVs and CPE score]; *P*: 0.004 (univariate), 0.055 (multivariate).

95% CI −0.01,0.13] and higher current CD4 cell counts [estimate for CD4 count 351 to 500 vs. ≤350: 0.03; 95% CI −0.01, 0.06; estimate for CD4 cell count >500 vs. ≤350: 0.04; 95% CI −0.01, 0.08]. Positive HCV antibody continued to be associated with a lower NPZ3 score [estimate −0.15; 95% CI −0.24, −0.06].

The same multivariate model (same covariates) was run using a dichotomous rather than a continuous CPE score to examine the role of particular CPE thresholds on NPZ3 score. The estimate using a CPE threshold of 2.0 (>2.0 vs. ≤2.0) was 0.11 (95% CI 0.04, 0.18; $P = 0.002$) among participants with more than three antiretroviral drugs in the regimen and 0.02 (95% CI −0.05,0.08; $P = 0.6$) among participants with three antiretrovirals or less.

Discussion

Among our large study population of HIV-positive individuals on antiretroviral treatment who had vRNA less than 50 copies/ml, those taking regimens with more than three antiretroviral drugs and with better predicted CNS penetration had better neurocognitive outcomes, after adjusting for other potentially confounding factors, although the magnitude of this effect was not large. The same association was not seen among participants taking three antiretrovirals or less. One explanation for these findings is that the better penetrating more than three-drug regimens have more of an effect on neurocognitive functioning than the worse penetrating more than three-drug regimens; this same effect may not be as apparent among participants taking three-drug regimens or less. An additional explanation is that some people may require more than three antiretroviral drugs to reach sufficiently high drug penetration to treat HIV in the nervous system.

To provide a frame of reference for interpreting the magnitude of the CPE effect on neurocognitive outcome we compare it to the magnitude of the effect of nadir CD4 cell count, an important risk factor for HAND [5,19,20]. The impact of a one-unit increase in CPE on

neurocognitive outcome among participants taking more than three antiretroviral drugs (estimate: 0.07; $P = 0.004$) was similar in magnitude to the difference in outcome between participants with a nadir CD4 cell count above 200 vs. 200 cells/μl or less (estimate 0.06; $P = 0.08$). Our analyses suggest that careful selection of antiretroviral regimens could increase the CPE by at least one unit for many individuals, and may yield neurocognitive benefits proportionate to the differences seen in neurocognitive impairment between participants with and without an AIDS diagnosis. Improved neurocognitive function would be expected to have an impact on activities of daily living [21], including medication adherence [22,23], driving [24], and employment [25]. To put into context the level of neurocognitive impairment in this group of individuals, it should be noted that we recently found that 26% of 1160 ALLRT participants analyzed had mild-to-moderate impairment at their first visit, and 22% of 991 with at least one follow-up visit had sustained impairment [5].

To eliminate potential biases related to differences in antiretroviral regimen potency, indexed by residual plasma viremia, we limited the analysis to participants who had achieved viral suppression on their antiretroviral regimen (vRNA <50 copies/ml). In addition, we were able to use virologic suppression as a proxy for antiretroviral medication adherence; as participants were virally suppressed, we can, with reasonable certainty, state that these participants were consistently taking the medications that they reported as their regimen. In addition, participants in this analysis had similar CD4 cell counts regardless of CPE rank. These findings suggest that for participants experiencing neurologic impairment, a switch to a regimen with higher CNS penetration might assist neurologic recovery while maintaining a similar immunologic and virologic profile.

The present analysis has some other distinct advantages over prior analyses. Although other analyses used a cross-sectional study design [26], this analysis provides estimates both of antiretroviral regimen CPE and neuropsychologic outcome over time, and uses a repeated measures analysis method. Additionally, the number of participants included is much larger than in prior studies [17], which strengthens the robustness and potential generalizability of the results. Another clear benefit in this study was that the CPE was estimated using a ranking scale that has been successfully applied in other analyses among a variety of cohorts, worldwide [15,16,18,27]. Letendre *et al.* [15,16] have developed an adaptable approach to estimating the CNS penetration of available antiretroviral agents, including nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry inhibitors; the system also permits scoring of combination regimens. As described in Methods, this ranking system uses physicochemical, pharmacokinetic, and pharmacodynamic data to compare antiretrovirals. Although brain parenchymal extracellular concentrations of drugs have been measured by in-vivo microdialysis in animals [28], this is not feasible in humans. Instead, CSF drug concentrations serve as a surrogate measure of CNS pharmacokinetics. Pharmacodynamic data considered include a drug's ability to suppress viral load in CSF and improve neurocognitive performance [15]. The multidimensional, integrative nature of the system yields relative, rather than absolute, rankings. This flexible system is intended to be refined as new drugs and new pharmacokinetic and pharmacodynamic data become available.

Our analyses have limitations. Although many of our participants contributed data from more than one time point during antiretroviral therapy, the analytical technique we used did not assess improvement or decline in cognitive function over time, but rather the concurrent relationship between CNS penetration scores and cognitive function as measured by NPZ3 scores; we did not analyze changes in NPZ3 scores. Also, our data were limited to evaluations during treatment, and did not include pretreatment neurocognitive assessments that would be needed to evaluate whether the extent of improvement after initiating antiretroviral drugs is related to the regimen's CPE. Although our findings can be discussed in the context of current regimens and their relationship with neurocognitive performance, they cannot be used to assess changes in regimens and how these directly affect changes in neurocognitive status in a particular individual. In terms of generalizability, our cohort was enrolled at multiple sites in the United States and Puerto Rico and is composed primarily of males, whereas the HIV epidemic is expanding in women [29].

Conclusion

These findings suggest that optimizing regimens with higher CPE scores could yield improved neurocognitive function without sacrificing the benefits of ART use. These neurocognitive gains could be expected to provide longer term productivity and functional ability in our patients living with HIV infection; however, based on the small, yet statistically significant, magnitude of the effect, it is not completely clear what the extent of these changes would be. Such a strategy should be tested in randomized clinical trials in which groups of HIV-infected individuals with a greater likelihood of neurocognitive impairment (such as those with nadir CD4 cell count <200 cells/μl) might best be able to demonstrate improvement.

Acknowledgements

We would like to thank the study participants; without them we would be unable to present these data. We would also like to thank the ALLRT team and the staff who work at participating ACTG sites and laboratories. In addition,

we would like to thank Daniel R. Kuritzkes, MD for his helpful suggestions.

Work for this manuscript was supported by the following grants: NIH grants: 5 U01 AI38855 and 1 U01 AI068634, University of Washington AI069434, Washington University in St. Louis ACTU (021) AI069495, Neurologic AIDS Research Consortium NS32228, RO1 MH58076, P30 MH62512. In addition, the project described was supported by Award Number U01AI068636 from the National Institute of Allergy and Infectious Diseases and supported by National Institute of Mental Health (NIMH), National Institute of Dental and Craniofacial Research (NIDCR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

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K.W.: data analysis, created figures and tables, interpretation of findings, reviewed manuscript.

S.L.: study and conceptual design, interpretation of findings, contributed to manuscript development, edited manuscript.

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S.E.: assisted with data analysis, interpretation of findings, reviewed manuscript.

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