Title

COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk of Neurocognitive Impairment in Men Living With HIV.

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COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for HIV-associated Neurocognitive Impairment

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Abstract:	Objective The Val allele of the Val158Met single-nucleotide polymorphism of the catechol-o-methyltransferase gene (COMT) results in faster metabolism and reduced bioavailability of dopamine (DA). Among persons living with HIV (PLWH), Val carriers display neurocognitive deficits relative to Met carriers, presumably due to exacerbation of HIV-related depletion of DA. COMT may also impact neurocognition by modulating cardiometabolic function, which is often dysregulated among PLWH. We examined the interaction of COMT, cardiometabolic risk, and nadir CD4 on NCI among HIV+ men. Methods 329 HIV+ men underwent COMT genotyping and neurocognitive and neuromedical assessments. Cohort-standardized z-scores for body mass index, systolic blood pressure, glucose, triglycerides, and high-density lipoprotein cholesterol were averaged to derive a cardiometabolic risk score (CMRS). Neurocognitive impairment

	(NCI) was defined as demographically-adjusted global deficit score≥0.5. Logistic regression modelled NCI as a function of COMT, CMRS, and their interaction, covarying for estimated premorbid function, race/ethnicity, and HIV-specific characteristics. Follow-up analysis included the 3-way interaction of COMT, CMRS, and nadir CD4. Results Genotypes were 81 Met/Met, 147 Val/Met, and 101 Val/Val. COMT interacted with CMRS ($p=0.02$) such that higher CMRS increased risk of NCI among Val/Val ($OR=2.13$, $p<.01$), but not Val/Met ($OR=0.93$, $p>.05$) or Met/Met ($OR=0.92$, $p>.05$) carriers. Among Val/Val, nadir CD4 moderated the effect of CMRS ($p<.01$) such that higher CMRS increased likelihood of NCI only when nadir CD4<180. Discussion Results suggest a tripartite model by which genetically-driven low DA reserve, cardiometabolic dysfunction, and historical immunosuppression synergistically enhance risk of NCI among HIV+ men, possibly due to neuroinflammation and oxidative stress.

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March 29, 2019

Dear Dr. Volberding,

We thank you for the opportunity to submit a revised version of our manuscript. We have addressed all the editorial and reviewer comments (in bold) and have provided detailed responses below. We have also used red text to indicate sections that have been changed within the manuscript itself. We hope that you will find the revised manuscript substantively improved.

Reviewer #1:

In this manuscript, Saloner et al. investigated the interplay between COMT SNPs, cardiometabolic risk factors and nadir CD4 as risk factors for NCI in HIV-infected men. They observed that (a) higher cardiometabolic risk score increased the risk of NCI only among Val/Val carriers and that (b) this effect was evident only when nadir CD4 was <180 cells/mmc. These findings were confirmed also in the subgroup of patients with HIV-RNA <50 copies/mL. Taken together, these observations seem to suggest that genetically-driven low DA reserve, cardiometabolic dysfunction, and history of immunosuppression synergistically enhance risk of NCI and that antiretroviral treatment alone might not completely restore cognitive function.

The paper is well written. The results of the study are interesting and of relevance; moreover, data are accurately described and discussed. Limitation are adequately acknowledged.

Some minor issues should be addressed before publication:

1. The title should specify that results are obtained in a male population. For example, an alternative title could be: "COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for Neurocognitive Impairment in HIV-infected Men".

Response: We appreciate the suggestion to increase the specificity of our title, so we have changed it to *COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for Neurocognitive Impairment in Men Living with HIV*.

2. Abstract, results: Please report also percentages for the three genotypes of the COMT gene.

Response: We have now added percentages for *COMT* genotypes in the Abstract: "Genotypes were 81 (24.6%) Met/Met, 147 (44.7%) Val/Met, and 101 (30.7%) Val/Val."

3. Page 5, first paragraph: correct type error "verus" to "versus"

Response: Thank you for identifying this typographical error, we have now corrected it.

4. Table 1. Plasma and CSF viral load should be expressed as copies/mL and not cells/mL

Response: We have made the suggested change and plasma/CSF viral load is now expressed as copies/ml.

5. Table 2. I suppose that results are expressed as mean (SD) except for glucose (median - IQR?) and NCI (n, %). Please specify in the notes.

Response: Yes, glucose is expressed in terms of median [IQR] and NCI as N (%). We have now clarified this in the notes section of Table 2.

6. In my opinion, Table 3 is unclear:

a. I suppose that bold variables are statistically significant variables: this should be specified in the notes.

Response: We have now specified in the notes section of Table 3 that "bolded predictors are significant at $p<.05$."

b. I don't understand the variables "CMRS x Met/Met" and "CMRS x Val/Met". This result is not commented in the text.

Response: We apologize for the confusion. We have incorporated the results of these parameters into the main manuscript in order to enhance the clarity of our analyses (page 12).

Given that *COMT* genotype is a categorical variable with three levels, our regression analyses necessitate that we create two *COMT* parameters in order to capture the full effect of *COMT* on NCI. In order to accomplish this, we used the widely-employed technique of reference coding (West, Aiken, & Krull, 1996). We coded the high enzymatic activity Val/Val group as the reference level, which resulted in two *COMT* regression parameters, "Met/Met" and "Val/Met". As we mention in the Table 2 notes, the Met/Met and Val/Met parameters represent the change in likelihood of NCI when comparing the Met/Met and Val/Met groups, respectively, to the Val/Val reference group.

The same principles apply when generating regression parameters that represent interaction effects between a three-level categorical variable (i.e., *COMT*) and a continuous variable (i.e., CMRS; West et al., 1996). Thus, the "CMRS x Met/Met" parameter reflects how the effect of CMRS on NCI changes when shifting from the Val/Val reference group to the Met/Met group. Similarly, the "CMRS x Val/Met" parameter reflects how the effect of CMRS on NCI changes when shifting from the Val/Val reference group to the Val/Met group.

West, S. G., Aiken, L. S., & Krull, J. L. (1996). Experimental personality designs: analyzing categorical by continuous variable interactions. *J Pers, 64*(1), 1-48.

c. I suppose that the variable "detectable plasma" refers to "detectable plasma viral load": this should be specified.

Response: We have now changed "detectable plasma" to "detectable plasma viral load."

d. Notes "f-g" are not correct, note h is lacking.

Response: Thank you for noticing this error. We have corrected the superscripts in Table 3.

e. Why other variables that have been associated with NCI in many other studies (such as age, education, AIDS diagnosis, substance use, BDI score and CSF viral load in the subgroup of patients with an available sample) are not considered in the multivariate model?

Response: We agree that it is important to consider the possible effects of additional factors that may impact NCI, particularly in the context of HIV. Our rationale for covariate selection is described in the Statistical Analyses section (page 10). In order to account for variables that may potentially confound the effects of *COMT* on NCI, we selected covariates based on variables that significantly differed across *COMT* groups (i.e., WRAT and race/ethnicity). Age and education adjustments are also built into the neuropsychological test T-scores on which the cognitive outcomes are based. Additionally, because our study is in the context of HIV-infection, we included standard indicators of HIV disease severity that have been consistently linked to neurocognition in the modern era of antiretroviral therapy (i.e., nadir/current CD4 counts, antiretroviral therapy use, plasma viral load). We did not include AIDS diagnoses or CSF viral load as covariates because they are highly collinear (*p*s <.0001) with nadir/current CD4 count and plasma viral load, respectively, and we did not have CSF viral loads on all participants. For non-HIV-specific variables, BDI scores, lifetime substance use diagnoses, age, and education did not differ across *COMT* groups and were therefore not considered in our multivariable models.

7. In the abstract, the authors report that "higher CMRS increased risk of NCI among Val/Val (OR=2.13, p<.01), but not Val/Met (OR=0.93, p>.05) or Met/Met (OR=0.92, p>.05) carriers". However, these results (OR and p values) are not reported nor in the results section of the main text neither in table 3 or figure 1

Response: Per this recommendation, we now include these results in the main text (page 13). These results are also included in the figure caption for Figure 1.

8. Among the limitations, it should be mentioned also the cross sectional design of the study.

Response: We have now acknowledged the cross-sectional design of the study as a limitation (page 17): "…the cross-sectional and associative nature of our data prevent us from drawing causal inferences, especially about the relationship between NCI and CMRS in the context of genetic and HIV disease history predictors."

Reviewer #2:

The manuscript entitled "COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for HIV-associated Neurocognitive Impairment" approaches an interesting topic in HIV infection, which is the search of correlates that help understand the appearance of HIV-associated neurocognitive impairment. Specifically, this work focuses on the investigation of a genetic marker, the COMT Val158Met polymorphism, which is analyzed in combination with environmental/medical factors, such as the cardiometabolic status and the nadir CD4 count. Authors find explaining interactions among them that show connections with neurocognitive impairment at different levels. The results emphasize the relevance of considering both genetic and environmental factors in the assessment of risk/protective factors of HIV-associated neurocognitive dysfunction. Study data appear to be analyzed adequately and most information properly presented. The manuscript could be accepted for publication, although some changes should be applied before in the text.

Specific comments:

Abstract

1. Abbreviation of neurocognitive impairment (NCI) is not correctly presented.

Response: We have corrected this in the Abstract accordingly.

2. Percentages should be added to frequencies of allele profiles.

Response: We have now added percentages to complement *COMT* group sample sizes.

Introduction

3. Citations for prevalence of NCI should be optimized. References 1 and 2 appear to be overlapped. Reference 3 is not a work focused on NCI prevalence. I recommend to provide representative studies that investigate specifically prevalence or widely frequency of NCI.

Response: We have replaced References 2 and 3 with a more representative study examining the prevalence of NCI/HAND in the Multicenter AIDS Cohort Study (MACS; Sacktor et al., 2016).

Sacktor, N., Skolasky, R. L., Seaberg, E., Munro, C., Becker, J. T., Martin, E., . . . Miller, E. (2016). Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. *Neurology, 86*(4), 334-340. doi:10.1212/wnl.0000000000002277

4. There are some prior works that demonstrated the role of nadir CD4 cell count as a predictor of HIV-associated NCI previously to reference 41.

Response: We have augmented the Introduction (page 6) with the following references that provide earlier documentation of the relationship between nadir CD4 and HIV-associated NCI.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., . . . Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *Aids, 21*(14), 1915-1921. doi:10.1097/QAD.0b013e32828e4e27

Tozzi, V., Balestra, P., Lorenzini, P., Bellagamba, R., Galgani, S., Corpolongo, A., . . . Narciso, P. (2005). Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: Results from an urban observational cohort. *J Neurovirol, 11*(3), 265-273. doi:10.1080/13550280590952790

Methods

5. GDS is chosen as method for determination of NCI, however, no discussion or justification about this decision is provided. Why was not the Frascati proposal used for this establishment? In fact, the second reference cited when GDS is presented recommends clinical rating classification as a more sensitive method to detect subtle forms of impairment.

Response: We appreciate the comment and have expanded our Methods (pages 9 and 10) to provide a rationale for selecting the GDS approach to classifying NCI. As the Reviewer points out, there are some subtle differences between the clinical ratings (CR) approach, which aligns with the Frascati criteria, and the GDS approach. Both approaches have been advanced by our co-author Dr. Robert Heaton, who was also part of the Frascati panel. The second reference cited, Blackstone et al. (2012), is a prior work from our group that established that the GDS is a more conservative method than CR for establishing NCI, yet also virtually ensures that the CR-based criterion for NCI is met (<1% of individuals were impaired by the GDS method and not the CR method). This GDS approach has been widely employed in neuroHIV research, in part because the process of computing a GDS and applying the 0.5 impairment cut-point is more readily accomplished and digestible than using the CR algorithm (see appendix of (Woods et al., 2004)), which could be subject to computational errors and can subsequently lead to inflated discrepancies between the GDS and CR (Saloner & Cysique, 2017). Furthermore, the complex Woods et al. (2004) algorithm is applied inconsistently (or not at all), particularly regarding how one applies a 1 SD cutoff for ability domains with variable numbers of component tests. As Blackstone et al. note, without an independent "gold-standard" indicator of HIV-associated NCI, we cannot claim that the GDS under-classifies NCI or that the CR approach over-classifies NCI. Rather, we acknowledge that both approaches demonstrate strong construct validity because they both relate to greater HIV disease severity and functional deficits, with the GDS having an added benefit of being more easily replicated by other research groups.

6. Reference for BDI should be added to text.

Response: The BDI is now referenced in the text (page 10).

Results

7. Effect size analyses by Cohen's d are presented in Statistical Analyses but later in Results there is only a value in reference to them. Further information about the results from those useful complementary tests should be provided.

Response: We have modified the Statistical Analyses section (page 10) to clarify that Cohen's *d* statistics are presented only for statistically significant pair-wise differences. Our analyses examining *COMT* group differences (Tables 1 and 2) revealed only two statistically significant pairwise differences for continuous outcomes that can be used to generate a Cohen's *d* statistic (i.e., WRAT scores: Met/Met vs. Val/Val [d=0.40; p=.007]; diastolic blood pressure: Met/Met vs. Val/Met [d=0.37; p=0.02]). These two Cohen's *d* estimates are presented in the Results (page 12).

8. There were relevant differences in the demographic characteristics of the sample, specifically in premorbid intelligence and ethnicity/race. Was any statistical method applied to adjust or correct the weight of those variables in the study outcomes?

Response: As the Reviewer notes, *COMT* groups differed with respect to race/ethnicity and estimated premorbid verbal IQ, as measured by the WRAT. In order to account for these group differences, we included WRAT scores and race/ethnicity as covariates in our multivariable logistic regression models (see Table 3). We have now reiterated in the results section (page 12) that we included relevant covariates in our regression models in order to assure the readers that we considered potential confounding factors.

9. Citation of Table 1 in text is linked to a Cohen's d result, but no information about effect sizes is provided in that table.

Response: We apologize for the confusion. We did not intend to imply that Cohen's *d* results would be displayed in Table 1. As we describe in our response to item 15 (below), we have modified the Results section (page 11) to properly present Table 1 in the text.

Discussion

10. The finding about a specific nadir cutoff revealing differences for NCI is really interesting (<180 cells/mm3). Previous published works have found certainly similar values when investigating the development of HIV-associated NCI. Examples are Ellis et al, 2011 and Muñoz-Moreno et al, 2014. Discussion about potential connections with those other findings should be incorporated in text.

Response: The Discussion has been expanded to include a comparison of our findings to the Ellis and Muñoz-Moreno articles (page 16). In addition to our study, these articles provide evidence that lower nadir CD4 not only increases the probability of NCI as an independent factor, but also that severe immunosuppression may reflect enhanced vulnerability to the detrimental neurocognitive effects of other clinically-relevant factors. Interestingly, Muñoz-Moreno et al. identified a nadir CD4 value of 225, which is fairly similar to our threshold of 180, as a relevant cutoff for optimizing the prediction of NCI in the context of other disease and treatment characteristics.

11. It is mentioned that authors' group has previously reported better executive functioning in Met/Met men with HIV infection compared to Val-carriers, but no citation is provided.

Response: We apologize for the oversight. The citation in question is now provided:

Bousman, C. A., Cherner, M., Glatt, S. J., Atkinson, J. H., Grant, I., Tsuang, M. T., & Everall, I. P. (2010). Impact of COMT Val158Met on executive functioning in the context of HIV and methamphetamine. *Neurobehav HIV Med, 2010*, 1-11. doi:10.2147/nbhiv.S8245

12. The fourth limitation presented appears to be very interesting. I encourage the authors to offer a more extended discussion on that point, rather than stating it as a limitation, actually. I would suggest the same for limitation 5 since I do believe that the selection of the method for cardiometabolic assessment was really appropriate.

Response: Per this recommendation, our discussion on "omics" analyses is no longer explicitly described as a limitation. Rather, we have expanded the Discussion (page 18) to note how the complexity and richness of DA-related biological data is well-suited to an "omics" approach that considers how multi-level genetic clusters can improve understanding of HIV-related neuropathogenesis.

We have also removed limitation 5. Given that we already provide a detailed discussion of the merits of our cardiometabolic assessment on page 15, we have not provided any additional commentary on our method of cardiometabolic assessment.

13. I relevantly miss some discussion about interventional proposals in the last paragraph of the Discussion. I would recommend to present or suggest some interventional approach since the study is now essentially based on a limited assessment perspective.

Response: The Reviewer raises an important point about considering future interventional approaches that may help address the risk factors identified in the present study. We have expanded the last Discussion paragraph (page 19) to note that adjunctive, nonpharmacological behavioral interventions, specifically exercise and improved sleep, have the potential to improve DA function, cardiometabolic health, and neurocognitive function in the context of HIV.

References

14. There are mistakes in the citation style.

Response: As suggested by the *JAIDS* author guidelines, we have set the EndNote reference style output to *JAMA*.

Tables and Figures

15. Table 1 should be properly presented in text.

Response: We have added the following sentence to the *Participants* section of the Results: "Table 1 presents COMT group differences in demographic and clinical characteristics."

16, b in the legend of Table 1 seems not to represent the information indicated.

Response: The information for superscript b represents the sample size for participants with available CSF viral load data. The superscript note is now written as: "[b]CSF viral load values available for a subset of participants: Met/Met (n=60), Val/Met (n=118), Met/Met (n=82)"

17. BDI score is displayed in Table 1 but later in legend it refers to BDI-II.

Response: The correct abbreviation is BDI. We have corrected the legend accordingly.

18. In Table 2 a reminder of the method for definition of neurocognitive impairment could be incorporated for an easier interpretation of the results.

Response: Thank you for the suggestion. We have added an additional superscript to Table 2: "[c]Neurocognitive impairment defined as global deficit score ≥ 0.5"

19. In Tables and Figures abbreviations and full words are indistinctly used; the same terms should be strictly used (e.g., Cardiometabolic risk score, CMRS, global deficit score, NCI, etc.).

Response: We have updated Tables and Figures to ensure consistency across terms.

Sincerely,

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Abstract

Objective: The Val allele of the Val158Met single-nucleotide polymorphism of the catechol-o-methyltransferase gene (*COMT*) results in faster metabolism and reduced bioavailability of dopamine (DA). Among persons living with HIV (PLWH), Val carriers display neurocognitive deficits relative to Met carriers, presumably due to exacerbation of HIV-related depletion of DA. *COMT* may also impact neurocognition by modulating cardiometabolic function, which is often dysregulated among PLWH. We examined the interaction of *COMT*, cardiometabolic risk, and nadir CD4 on neurocognitive impairment (NCI) among HIV+ men.

Methods: 329 HIV+ men underwent *COMT* genotyping and neurocognitive and neuromedical assessments. Cohort-standardized z-scores for body mass index, systolic blood pressure, glucose, triglycerides, and high-density lipoprotein cholesterol were averaged to derive a cardiometabolic risk score (CMRS). NCI was defined as demographically-adjusted global deficit score≥0.5. Logistic regression modelled NCI as a function of *COMT*, CMRS, and their interaction, covarying for estimated premorbid function, race/ethnicity, and HIV-specific characteristics. Follow-up analysis included the 3-way interaction of *COMT*, CMRS, and nadir CD4.

Results: Genotypes were 81 (24.6%) Met/Met, 147 (44.7%) Val/Met, and 101 (30.7%) Val/Val. *COMT* interacted with CMRS (p=0.02) such that higher CMRS increased risk of NCI among Val/Val (OR=2.13, p<.01), but not Val/Met (OR=0.93, p>.05) or Met/Met (OR=0.92, p>.05) carriers. Among Val/Val, nadir CD4 moderated the effect of CMRS (p<.01) such that higher CMRS increased likelihood of NCI only when nadir CD4<180.

Discussion: Results suggest a tripartite model by which genetically-driven low DA reserve, cardiometabolic dysfunction, and historical immunosuppression synergistically enhance risk of NCI among HIV+ men, possibly due to neuroinflammation and oxidative stress.

Keywords: NeuroAIDS, Catechol O-Methyltransferase, HIV associated neurocognitive disorders, metabolic syndrome, dopamine, immunosuppression

Body Word Count: 3742
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Figures: 2

COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for Neurocognitive Impairment in Men Living with HIV

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Oral presentation delivered at the Interational Neuropsychological Society (INS) Annual Conference, New York, NY (2019, February).

Abstract

Objective: The Val allele of the Val158Met single-nucleotide polymorphism of the catechol-o-methyltransferase gene (*COMT*) results in faster metabolism and reduced bioavailability of dopamine (DA). Among persons living with HIV (PLWH), Val carriers display neurocognitive deficits relative to Met carriers, presumably due to exacerbation of HIV-related depletion of DA. *COMT* may also impact neurocognition by modulating cardiometabolic function, which is often dysregulated among PLWH. We examined the interaction of *COMT*, cardiometabolic risk, and nadir CD4 on neurocognitive impairment (NCI) among HIV+ men.

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Results: Genotypes were 81 (24.6%) Met/Met, 147 (44.7%) Val/Met, and 101 (30.7%) Val/Val. *COMT* interacted with CMRS (p=0.02) such that higher CMRS increased risk of NCI among Val/Val (OR=2.13, p<.01), but not Val/Met (OR=0.93, p>.05) or Met/Met (OR=0.92, p>.05) carriers. Among Val/Val, nadir CD4 moderated the effect of CMRS (p<.01) such that higher CMRS increased likelihood of NCI only when nadir CD4<180.

Discussion: Results suggest a tripartite model by which genetically-driven low DA reserve, cardiometabolic dysfunction, and historical immunosuppression synergistically enhance risk of NCI among HIV+ men, possibly due to neuroinflammation and oxidative stress.

Keywords: NeuroAIDS, Catechol O-Methyltransferase, HIV associated neurocognitive disorders, metabolic syndrome, dopamine, immunosuppression

Introduction

Combination antiretroviral therapy (cART) prolongs life expectancies for persons living with HIV (PLWH); however, neurocognitive impairment (NCI) remains highly prevalent[1,2]. It is important to identify discrete neuropathological mechanisms that predict NCI in PLWH given that NCI can translate to negative and costly everyday functioning outcomes, including unemployment and poor cART adherence[3,4]. However, identifying these mechanisms has proven challenging[5-7] because PLWH are a heterogeneous group whose neurocognition may be directly impacted by HIV, but also by comorbidities and genetic predispositions that enhance vulnerability to neural injury[6,8,9].

PLWH are at greater risk of cardiometabolic complications (i.e., hypertension, dyslipidemia, diabetes, and obesity) possibly due to HIV-related accelerated biological aging and iatrogenic consequences of cART[10,11]. Cardiometabolic risk contributes to NCI by triggering an array of neuro-compromising processes, including increased blood-brain-barrier permeability, chronic inflammation, and endothelial dysfunction[12-16]. Furthermore, cardiometabolic risk factors predict imaging biomarkers of white matter and neurochemical abnormalities among PLWH[17,18]. While cardiometabolic risk factors increase risk of NCI in successfully treated PLWH, they are neither necessary nor sufficient to predict NCI. Thus, susceptibility to the contribution of cardiometabolic risks may be moderated by individual differences in resilience against HIV-related CNS dysfunction.

One factor that could partially explain NCI among PLWH is dopamine (DA) bioavailability. HIV results in exposure to neurotoxic proteins Tat and gp120 that

damage frontostriatal regions rich in DA[19,20]. Post-mortem studies demonstrate decreased frontostriatal concentrations of DA and downregulated gene expression of DA receptors in HIV-infected versus HIV-uninfected persons, and that dysregulation of DA pathways relates to greater HIV disease severity (e.g., HIV RNA level, nadir CD4) and neurocognitive deficits among PLWH[21-25].

The erosion of DA homeostasis in PLWH has prompted research on catechol-o-methyltransferase (COMT)[6], a functionally diverse enzyme responsible for metabolism of DA, particularly in the prefrontal cortex (PFC). Neurons exposed to macrophage-propagated HIV show increased mRNA expression of *COMT* and decreased expression of neuronal and synaptic proteins, suggesting that higher levels of COMT in HIV may contribute to DA and neurocognitive dysfunction. In further support of this theory, treatment of HIV-exposed neurons with a COMT inhibitor, Tolcapone, effectively reduced *COMT* expression and restored neuronal and synaptic integrity[26]. The Val158Met (rs4680) single nucleotide polymorphism (SNP) of the *COMT* gene encodes differential levels of COMT enzymatic activity, with the Met allele resulting in 40% less activity, and therefore greater DA bioavailability, than the Val allele[27]. The Met allele has been linked to enhanced neural activation and neurocognitive functioning in PLWH[28,29], possibly due to resilience against HIV-related depletion of DA.

Some literature suggests that COMT also operates within cardiometabolic pathways. COMT catalyzes the methylation of catechol estrogens into 2-methoxyestradiol[30], which reduces risk of diabetes, hypertension, and obesity[31-34]. However, COMT activity produces a precursor to homocysteine, which may increase risk of cardiovascular disease, and Val carriers have significantly higher blood levels of

total homocysteine than Met homozygotes[35-37]. Furthermore, lower central DA tone has been linked to obesity and markers of metabolic syndrome, and DA receptor neurotransmission is reduced in obese humans and animals[38-40]. While greater COMT activity associated with the Val allele may protect against cardiometabolic disorders through increased production of 2-methoxyestradiol, reduced COMT activity associated with the Met allele may also confer protection against cardiometabolic disorders by enhancing DA tone and limiting the accumulation of homocysteine. Although the influence of *COMT* on cardiometabolic health is complex, these mechanisms suggest that *COMT* may serve a multifactorial role in the neuropathogenesis of HIV-related NCI through the modulation of cardiometabolic risk and DA bioavailability.

Our first aim is to examine the independent and interactive effects of *COMT* and cardiometabolic risk on NCI. Given the putative neuroprotective effect of the Met allele in PLWH, we hypothesize that Val/Val carriers with high cardiometabolic risk will have higher rates of NCI compared to others because they are most vulnerable to the deleterious impact of cardiometabolic risk factors on the brain. Because NCI has been more reliably linked to nadir versus current CD4 count in the cART era[1,41-43], we will also examine the role of nadir CD4 in the conditional relationships between *COMT,* cardiometabolic risk, and NCI. We hypothesize that lower nadir CD4 counts will increase likelihood of NCI regardless of *COMT* and cardiometabolic risk, but will make a larger contribution to NCI in Val/Val carriers with high cardiometabolic risk.

Methods

Participants and Procedure

Participants were 329 HIV+ men who underwent *COMT* genotyping through NIH-funded research studies coordinated by the HIV Neurobehavioral Research Program (HNRP) at the University of California, San Diego. Of the 329 participants, 76 were enrolled in the Translational Methamphetamine AIDS Research Center (TMARC), a NIDA-funded HNRP cohort study focusing on the central nervous system effects of HIV and methamphetamine. The other 253 participants were enrolled in the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study. All studies were approved by local Human Subjects Protection Committees and all participants provided written informed consent. Exclusion criteria were: 1) diagnosis of psychotic or mood disorder with psychotic features, neurological or medical condition that may impair neurocognitive functioning, such as traumatic brain injury, stroke, epilepsy, hepatitis C, or advanced liver disease; 2) lifetime diagnosis of methamphetamine or cocaine use disorder; 3) low verbal IQ as estimated by a Wide Range Achievement Test[44] (WRAT) reading subtest score <70; 4) evidence of intoxication by positive urine toxicology for illicit drugs (except marijuana) or Breathalyzer test for alcohol on the day of testing; and 5) being female. We restricted our sample to men because sexually dimorphic effects of *COMT* on brain function have been reported[45,46] and there were insufficient numbers of women participants in the parent studies to support separate analyses. Lifetime cocaine or methamphetamine use disorder, even remote, was exclusionary in order to eliminate potential confounding effects of stimulant-induced alteration of dopaminergic signaling.

Neuromedical Assessment

All participants underwent a comprehensive neuromedical assessment and non-fasting blood draw. Detailed history of medical and antiretroviral (ARV) use was

collected and ARV treatment status was coded as currently on, past use, or never used. HIV infection was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and CD4+ T cell count (flow cytometry) were performed at each site's certified clinical laboratory. HIV viral load in plasma and CSF were measured using reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostics, Indianapolis, IN), with a lower limit of quantitation (LLQ) of 50 copies/ml). HIV viral load was dichotomized as detectable vs. undetectable at the LLQ of 50 copies/ml.

Cardiometabolic Risk Assessment

Non-fasting levels of serum glucose, plasma triglycerides, and plasma total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels were assayed by standard protocols at each site's clinical laboratory. Blood pressure (BP) was measured in the seated position with an automated sphygmomanometer and body mass index (BMI) was calculated from measured weight and height. Our primary predictor of interest was a continuously scaled, composite cardiometabolic risk score (CMRS)[47] based on the five components of metabolic syndrome outlined by the Adult Treatment Panel[48] including obesity, elevated BP, elevate blood glucose, elevated triglycerides, and reduced (HDL) cholesterol. Cohort-standardized z-scores for BMI, systolic BP, glucose, triglycerides, and HDL cholesterol (inverse polarity) were averaged to generate our CMRS. A CMRS was derived from 4 of the 5 component z-scores for participants who were either missing HDL (n=50) or triglycerides (n=4) values.

COMT Genotyping

For participants enrolled in TMARC, DNA for genotyping was isolated from stored whole blood or peripheral blood mononuclear cells (PBMCs) using the Qiagen QIAamp DNA Mini Kit (Qiagen, Valencia, CA). COMT Val158Met (rs4680) SNP was assayed using an array that included SNPs associated with catecholaminergic genes[49]. For participants enrolled in CHARTER, DNA for genotyping was extracted from PBMCs using PUREGENE (Gentra Systems, Inc, Minneapolis, MN). All samples were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0TM[50].

Neurocognitive Assessment

All participants completed a comprehensive and standardized neurocognitive assessment across seven neurocognitive domains commonly impacted by HIV[1,51]. Test scores were adjusted for known demographic influences (i.e., age, education, and race/ethnicity) on neurocognitive performance[52-54]. Deficit scores that give differential weight to impaired over normal performance were calculated for each domain and averaged to derive a global deficit score (GDS) ranging from 0 (normal) to 5 (severe). Consistent with prior studies, neurocognitive status was classified as impaired (NCI) vs. unimpaired using a validated cut-point of GDS $\geq$ 0.5[51,55] The GDS is easier to compute, more clearly operationalized (e.g., Frascati criteria do not specify how to apply a 1 SD cutoff to define "impairment" of ability domains with variable numbers of measures) and a more conservative approach to classifying NCI as compared to the clinical ratings algorithm used in Frascati criteria for HIV-associated Neurocognitive Disorders; however, an individual classified as impaired via GDS $\geq$ 0.5 is essentially guaranteed to meet the NCI aspect of Frascati criteria[55].

Psychiatric Assessment

Current mood symptoms were assessed using the Beck Depression Inventory (BDI) version one or two[56]. The computer-based Composite International Diagnostic Interview (CIDI)[57] was administered to determine DSM-IV diagnoses of current and lifetime substance use disorders (SUD) and Major Depressive Disorder (MDD).

Statistical Analysis

COMT group differences in demographics, HIV disease, neuropsychiatric, cardiometabolic, and neurocognitive variables were examined using ANOVAs, Kruskal-Wallis tests, and Chi-square statistics as appropriate. To follow-up on significant omnibus results, pair-wise comparisons were conducted using Tukey's Honest Significant Difference (HSD) tests for continuous outcomes or Bonferroni-corrections for categorical outcomes[58]. Cohen's *d* statistics are presented for estimates of effect size for statistically significant pair-wise differences. Logistic regression examined the univariate relationship between CMRS and NCI.

Next, we used multivariate logistic regression to model our NCI classification as a function of *COMT*, CMRS, and their interaction. *COMT* genotype was reference coded[59] with the high enzymatic activity Val/Val group as the reference. WRAT, race/ethnicity, nadir CD4, current CD4, plasma viral load detectability, and ARV status were entered as covariates because they either significantly differed across *COMT* genotype or are known to influence neurocognition in the cART era[1,60]. A 3-way interaction term between nadir CD4**COMT**CMRS, as well as accompanying lower-order terms, was added in a follow-up model in order to explore the potential moderating effect of HIV-induced immunosuppression on the contributions of *COMT* and CMRS on NCI. Group

differences and logistic regression analyses were performed using *JMP Pro* version 12.0.1 (JMP®, Version <*12.0.1*>, SAS Institute Inc., Cary, NC, 1989-2007).

Exploratory analyses, stratified by *COMT* genotype, employed the Johnson-Neyman (J-N) technique[61,62] to compute any specific boundaries of nadir CD4 at which CMRS significantly predicted NCI. These boundaries are referred to as regions of significance. Compared to simple slope analyses that describe the effect of a predictor (i.e., CMRS) at fixed levels of a continuous moderator (i.e., nadir CD4), the J-N technique identifies the full range of moderator values for which the predictor slope is statistically significant. Region of significance analyses adjusted for false discovery rate[63] and were computed using the *jtools* package in *R* statistical software (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

Table 1 presents *COMT* group differences on demographic and clinical characteristics. *COMT* distribution across the 329 participants (age: M=44.0, SD=8.97, education: M=14.1, SD=2.34) was 81 (24.6%) Met/Met, 147 (44.7%) Val/Met, and 101 (30.7%) Val/Val. Genotype distribution was consistent with Hardy-Weinberg equilibrium in the full sample (χ^2=3.49, *p*=0.06) and within each race/ethnicity group (*p*s>.11). However, genotype frequency differed significantly by race/ethnicity (χ^2= 11.24, *p*=0.02) with non-Hispanic White participants more likely to carry a Met allele than non-Hispanic Black participants (χ^2=8.75, *p*=0.003). *COMT* groups were comparable across most demographic, psychiatric, and HIV disease characteristics, with the exception of estimated premorbid verbal IQ for which Met/Met displayed significantly higher WRAT

scores than Val/Val (*d*=0.40, *p*=0.007). Most participants experienced cART-induced immune reconstitution, as evidenced by active ARV use (76%) and markedly higher current CD4 counts (median=458 cells/mm^3) compared to nadir CD4 counts (median=180 cells/mm^3). Half the sample (51%) had detectable levels of plasma viral RNA at a limit of detection of 50 copies per ml.

COMT, Cardiometabolic Risk, and NCI

Table 2 presents *COMT* group differences on cardiometabolic and neurocognitive variables. Met/Met had significantly higher diastolic blood pressure than Val/Met (*d*=0.37, *p*=0.02) but not Val/Val. *COMT* groups did not differ significantly on any other cardiometabolic risk parameters, including the composite CMRS (*F*=0.09, *p*=0.91). Similarly, *COMT* groups did not differ significantly on GDS (*F*=0.17, *p*=0.84) or frequency of NCI (χ2=2.39, *p*=0.30), with rates ranging from 32% (Val/Met) to 42% (Val/Val). Although greater CMRS increased likelihood of NCI, this relationship was also not significant (OR=1.12, 95%CI [0.89-1.40], *p*=0.34).

COMT and CMRS Interaction

Table 3 presents estimates for the multivariate logistic regression modelling NCI as a function of *COMT*, CMRS, and NCI, covarying for WRAT scores, race/ethnicity, and HIV disease characteristics. The overall model was significant (χ^2(13,329)=392.68, *p*=0.001). A significant omnibus interaction between *COMT* and CMRS was detected (χ^2(2,329)=7.93, *p*=0.02) such that higher CMRS levels significantly increased likelihood of NCI among Val/Val (OR=2.13, p<.01), yet the deleterious effect of CMRS on NCI was significantly attenuated in Met/Met (interaction of CMRS x Met/Met [compared to Val/Val]: ORR=0.42, *p*<.05) and Val/Met (interaction of CMRS x Val/Met

[compared to Val/Val]: ORR=0.43, *p*<.05). Specifically, CMRS did not significantly predict NCI among Met/Met (OR=0.92, p>.05) or Val/Met (OR=0.93, p>.05) carriers (Figure 1). Lower WRAT, lower nadir CD4, and detectable HIV RNA significantly increased probability of NCI (*p*s<.05).

Conditional Role of Nadir CD4

To determine whether HIV disease severity influenced the interactive effects of *COMT* and CMRS on NCI, we expanded our model with terms capturing the 3-way interaction between nadir CD4, *COMT*, and CMRS. A significant 3-way interaction was detected between nadir CD4, *COMT*, and CMRS (χ^2(2,329)=8.86, *p*=0.01). Nadir CD4 did not significantly alter the null associations between CMRS and NCI among Val/Met and Met/Met. In Val/Val, nadir CD4 significantly moderated the deleterious effect of CMRS on NCI (for 50-unit increase: ORR=0.53, 95%CI [0.32, 0.81], *p*=0.008). In order to inspect changes in the slope of CMRS on NCI due to different nadir CD4 counts, we applied the J-N technique. In Val/Val, CMRS significantly increased likelihood of NCI (i.e., lower bound of CMRS slope>0) at nadir CD4 counts below 180 (Figure 2). Conversely, CMRS did not significantly predict NCI in Val/Val for nadir CD4 counts at or above 180.

To focus on a clinically relevant subgroup, we applied the 3-way interaction model in participants who were currently using cART and had undetectable HIV RNA (n=155). Results in this virologically suppressed subgroup did not differ from those in the entire study sample, with *COMT*, CMRS, and nadir CD4 significantly interacting to predict NCI (χ^2(2,150)=10.25, *p*=0.006).

Discussion

Dopaminergic dysregulation, cardiometabolic dysfunction, and low nadir CD4 counts (i.e., advanced HIV-induced immunosuppression) are putative risk factors for NCI in the context of HIV. In contrast to most neuroAIDS studies that examine independent effects of risk factors on NCI, this study also examined interactions of cardiometabolic risk, *COMT,* and nadir CD4 in order to address the complex interplay of these risk factors. Although neither *COMT* nor CMRS correlated univariably with NCI, higher CMRS significantly increased probability of NCI in Val/Val individuals. Furthermore, CMRS effects on neurocognitive function in Val/Val carriers were moderated by nadir CD4: higher CMRS increased probability of NCI only in participants with nadir CD4 counts below 180. These findings remained significant in patients with fully-suppressed HIV on cART, underscoring the relevance of these genetic and environmental risk factors for NCI for even the most successfully treated PLWH.

Our group has previously reported better executive function among Met/Met, compared to Val-carriers, in HIV+ men[29]. In contrast, the Multicenter AIDS Cohort Study found no main effects of *COMT* or interactive effects with stimulant use and current CD4 on neurocognitive performance in predominantly male (87%-100%) samples[64,65]. In our study, *COMT* did not univariably relate to frequency of NCI, which, consistent with prior GDS-based estimates of NCI in PLWH[51,55], was 36% across the entire study sample. We may not have detected a univariable relationship between *COMT* and NCI because individual SNPs often exhibit modest associations with behavioral phenotypes[66]. Given that *COMT* pleiotropically influences multiple neurobiological processes, the study of moderating environmental variables can help explain under which conditions the neurocognitive effects of *COMT* are most salient.

Our results support a gene x environment interaction approach, as the putatively harmful effect of the Val allele only appeared under environmental conditions of high cardiometabolic burden and low nadir CD4 counts. Similar interactive effects of *COMT* and cardiovascular risk have been previously reported in healthy adults, with Val carriers demonstrating steeper declines in episodic memory compared to Met/Met individuals only at elevated levels of pulse pressure[67]. While the effects of cardiometabolic comorbidities on poor neurocognition are not unique to PLWH, cardiometabolic abnormalities may be particularly disruptive in PLWH given their high prevalence and potential to combine with other HIV-related brain insults to synergistically deplete cognitive reserve[68]. Although studies of cardiometabolic risk often dichotomize individual cardiometabolic conditions based on thresholds of clinical laboratory values[69], we modelled cardiometabolic risk as a standardized, continuous variable. This approach is statistically advantageous because continuous predictors preserve power and precision[70]. Moreover, thresholds for dichotomizing cardiometabolic conditions are imprecisely defined and overlook incremental relationships between cardiovascular disease outcomes (e.g., stroke) and health indicators (e.g., BP)[71]. Importantly, continuous cardiometabolic risk scores inversely relate to physical activity[47,72] and therefore, provide further evidence to advocate exercise in its neurocognitive benefits for PLWH.

With respect to conditional effects of HIV-induced immunosupression, Levine et al.[65] did not detect interactions between current CD4 count and DA-related genes, including *COMT*, on neurocognitive performance. However, as the authors note, current CD4 may be a suboptimal indicator of HIV disease severity given that nadir CD4 is a

stronger predictor of NCI and brain integrity in the cART era[1,41,73]. Furthermore, lower nadir CD4, but not current CD4, is correlated with reduced DA transporter availability in the ventral striatum[25]. Our results indicating that lower nadir CD4 counts independently predict higher odds of NCI are consistent with the prior findings of Ellis et al.[41] that describe a monotonic relationship between lower nadir CD4 counts and higher odds of NCI, even in PLWH with viral suppression and minimal-to-moderate comorbidity burden. Importantly, we also demonstrate that nadir CD4 moderates the interactive effects of *COMT* and CMRS. The clinical impact of these findings is highlighted by the substantial portion (55%) of Val/Val participants with nadir CD4 counts at or below 180, a range at which our region of significance analysis indicates a heightened vulnerability to the deleterious neurocognitive effects of cardiometabolic risk. In a prior investigation that implemented machine learning to generate predictive models for NCI, the predictive utility of viral load and duration of treatment were improved when nadir CD4 was less than 225[74], a threshold similar to that of the present study.

Some hypothesize that the relationship between cortical function and DA bioavailability follows an inverted U-shaped curve, with optimal neurocognition occurring at intermediate levels of DA signaling[75,76]. Within this framework, severe immunosuppression in PLWH may lead to persistently suboptimal levels of bioavailable DA even after successful immune reconstitution with cART. The slow rate of DA clearance conferred by the Met allele may protect against this shift, whereas the neurocognitive deficits present in Val/Val PLWH with high cardiometabolic burden may reflect an inability to compensate for reduced cognitive resources associated with DA dysfunction.

Although limitations in our data prevents us from investigating biological mechanisms that may underlie the interactive effects of *COMT*, CMRS, and nadir CD4 on NCI, we offer several plausible neurobiological interpretations. Chronic neuroinflammation is a hallmark feature of HIV-related CNS dysfunction[77]. Immunosuppression, cardiovascular disease, and metabolic syndrome are associated with increased levels of pro-inflammatory biomarkers in the periphery and in CSF, as well as neuroinflammation on magnetic resonance spectroscopy in PLWH[11,17,78-80]. Limited bioavailability of DA and epinephrine due to high enzymatic activity of COMT may also result in poor neuroinflammatory regulation because catecholamines play a pivotal role in modulating lymphocyte and inflammasome activity[81,82]. In addition to neuroinflammatory dysregulation, excessive formation of reactive oxygen species and endothelial dysfunction are neurotoxic processes associated with immunosuppression, cardiometabolic risk, and catecholamine metabolism[83-89]. While our data reflect the neurobehavioral consequences of genetically-driven low DA signaling, poor cardiometabolic health, and more severe HIV disease, studies at a cellular level are needed to elucidate the mechanisms of their interactions.

We acknowledge several limitations to this study. First, the cross-sectional and associative nature of our data prevent us from drawing causal inferences, especially about the relationship between NCI and CMRS in the context of genetic and HIV disease history predictors. Second, we lacked an HIV- uninfected comparison group, hindering our ability to determine the specificity of our findings to PLWH. However, by exploring the conditional effect of nadir CD4 with the J-N technique, we demonstrate how HIV disease severity in a clinically-relevant and well-represented range (i.e., nadir

CD4 <180) can modulate the effects of genetic and environmental risk factors for NCI. Third, our results focused on clinically informative risk factors for NCI that may inform future interventions targeting the maintenance of cardiometabolic health (e.g., exercise, diet, sleep) and dopaminergic therapy (e.g., COMT-inhibitors), but our sample comprised men only and therefore limits the applicability of our findings to women. Fourth, we studied the effects of only one variant of *COMT,* but not other DA-related genetic variants on NCI in PLWH. As is the case with theoretically-driven single SNP analyses, *COMT* may be in linkage disequilibrium with other SNPs in the DA pathway that could account for the presumed effects of *COMT*. "Omics" techniques that leverage rich, multi-leveled data (e.g., genetic, transcriptomic, epigenetic) may advance the characterization of complex and subtle HIV-related neurobiological phenotypes[6]. Given that multiple components of the DA signaling pathway (e.g., receptors, metabolic enzymes, transporters) can be quantified across multiple levels of analysis (e.g., host genetics, microRNA expression, imaging), an "omics" approach has the potential to uncover clusters of DA-related factors that track with intermediate biological phenotypes as well as disease and neurobehavioral endpoints (e.g., NCI).

Taken together, our findings suggest a tripartite model by which genetically-driven low DA reserve, cardiometabolic dysfunction, and history of immunosuppression synergistically enhance risk of NCI among HIV+ men. These interactive effects remain significant in virally suppressed participants receiving cART, suggesting that currently effective HIV treatment alone may not sufficiently mitigate neurocognitive dysfunction associated with the combination of genetic vulnerabilities, historically severe HIV-induced immunosupression, and cardiometabolic risk factors. In addition to cART,

adjunctive behavioral therapies that target modifiable lifestyle factors could be considered as a means to address this diverse combination of risk factors[90]. In particular, interventions to increase physical activity and/or reduce sleep disturbances may help stabilize DA function and cardiometabolic health, reduce inflammatory and oxidative stress burden, and subsequently ameliorate persisting neurocognitive deficits in HIV-infected patients[91-95].

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Figure Captions

Figure 1. Higher cardiometabolic risk scores significantly increase probability of neurocognitive impairment (NCI) in Val/Val participants (OR=2.13, $p<.01$), but do not relate to NCI in Val/Met (OR=0.93, $p>0.05$) or Met/Met (OR=0.92, $p>0.05$) participants.

Figure 2. Effect sizes (logits) of cardiometabolic risk scores (CMRS) on neurocognitive impairment (NCI) are plotted across nadir CD4 count for the Val/Val group. When the X-axis zero-line is included in the false discovery rate-adjusted confidence band, the effect of CMRS is not statistically significant at that nadir CD4 count. The region of significance occurs to the left of the dashed line, indicating that higher CMRS is significantly associated with greater likelihood of NCI only for nadir CD4 counts below 180.

Table 1. Demographic and clinical characteristics by COMT genotype (N=329)

Variable	Met/Met (n=81)	Val/Met (n=147)	Val/Val (n=101)	*p*
Demographics				
Age (years)	45.1 (9.69)	43.7 (9.09)	43.6 (8.16)	0.44
Education (years)	14.3 (2.54)	14.1 (2.39)	13.9 (2.1)	0.54
Estimated Verbal IQ (WRAT)	104.4 (11.41)	101 (11.3)	99.8 (11.76)	**0.02**[a]
Ethnicity				**0.02**[a]
Non-Hispanic White (n=245)	66 (81%)	110 (75%)	69 (68%)	
Non-Hispanic Black (n=33)	3 (4%)	12 (8%)	18 (18%)	
Hispanic (n=51)	12 (15%)	25 (17%)	14 (14%)	
HIV Disease Characteristics				
AIDS diagnosis	53 (65%)	89 (61%)	57 (56%)	0.47
Duration of HIV infection (years)	10.2 (7.83)	9.5 (6.44)	9.2 (6.3)	0.60
Current CD4 count (cells/mm^3)	517 (255.5)	470 (261.1)	457 (261.5)	0.27
Nadir CD4 count (cells/mm^3)	180 [63.5-305]	175 [44-297]	175 [55-297.5]	0.83
Plasma viral load				
Copies/ml (log_{10})	1.8 [1.7-3.3]	1.9 [1.7-3.7]	2.3 [1.7-3.9]	0.45
Detectable	42 (52%)	69 (47%)	57 (56%)	0.33
CSF viral load				
Copies/ml (log_{10})[b]	1.7 [1.7-1.7]	1.7 [1.7-2.2]	1.7 [1.7-2.4]	0.21
Detectable[b]	11 (18%)	34 (29%)	24 (29%)	0.24
ARV status				0.36
Currently on	67 (83%)	105 (71%)	77 (76%)	
Past use only	7 (9%)	16 (11%)	10 (10%)	
ARV naïve	7 (9%)	26 (18%)	14 (14%)	
Current regimen type				0.21
PI-based	31 (46%)	54 (51%)	42 (55%)	
NNRTI-based	27 (40%)	38 (36%)	30 (39%)	
PI/NNRTI-based	4 (6%)	11 (10%)	5 (6%)	
Other	5 (7%)	2 (2%)	0 (0%)	
Duration of current regimen (months)	12 [3-33]	13 [4-27]	12 [4-33]	0.96
Neuropsychiatric characteristics				
Lifetime any substance use disorder	38 (47%)	68 (46%)	51 (51%)	0.80
Alcohol	35 (43%)	57 (38%)	42 (42%)	0.79
Cannabis	16 (20%)	21 (14%)	18 (18%)	0.54
Opioid	0 (0%)	1 (1%)	0 (0%)	0.99
Major Depressive Disorder				
Lifetime	44 (54%)	72 (49%)	51 (51%)	0.74
Current	15 (19%)	19 (13%)	12 (12%)	0.41
BDI score	11.8 (9.57)	12.6 (10.14)	11.2 (9.32)	0.52

Note. Values presented as mean (SD), median [IQR], or N (%). WRAT= Wide-Range Achievement reading subtest; ARV= antiretroviral therapy; PI= Protease-inhibitor;

NNRTI= non-nucleoside reverse transcriptase inhibitor; BDI= Beck Depression Inventory

[a]Significant difference between Met/Met and Val/Val

[b]CSF viral load values available for a subset of participants: Met/Met (n=60), Val/Met (n=118), Met/Met (n=82)

Table 2. Cardiometabolic risk and neurocognitive performance by *COMT* genotype

Variable	Met/Met (n=81)	Val/Met (n=147)	Val/Val (n=101)	*p*
Cardiometabolic parameters				
Cardiometabolic risk score	0.01 (0.489)	-0.02 (0.548)	-0.01 (0.467)	0.91
Body mass index (kg/m^2)[a]	26.3 (4.42)	25.8 (4.37)	25.4 (4.46)	0.43
Systolic blood pressure (mm Hg)[a]	127 (14.13)	124.4 (15.41)	124.6 (14.76)	0.41
Diastolic blood pressure (mm Hg)[a]	79.3 (9.68)	75.8 (8.98)	76.2 (9.66)	**0.02**[b]
Total cholesterol (mg/dL)	196.8 (54.11)	184.6 (40.68)	192.2 (41.24)	0.12
High-density lipoprotein (mg/dL)[a]	41.8 (15.94)	42.2 (15.71)	44.5 (22.52)	0.59
Low-density lipoprotein (mg/dL)	111.8 (37.63)	100.2 (35.16)	106.8 (35.22)	0.10
Triglycerides (mg/dL)[a]	217.6 (149.22)	221.3 (140.91)	228.8 (158.63)	0.87
Glucose (mg/dL)[a]	94 [86-105.5]	92 [81-107]	92 [83-107.5]	0.87
Neurocognitive Performance				
Global deficit score	0.51 (0.52)	0.49 (0.58)	0.47 (0.48)	0.84
Neurocognitive impairment[c]	29 (36%)	47 (32%)	42 (42%)	0.30

Note. Values presented as mean (SD), median [IQR], or N (%).

[a]Cardiometabolic risk score component

[b]Significant difference between Met/Met and Val/Met

[c]Neurocognitive impairment defined as global deficit score ≥ 0.5

Table 3. Multivariable logistic regression predicting neurocognitive impairment

Predictor	B (SE)	*p*	OR[a]	OR 95% CI
Met/Met[b]	-0.15 (0.34)	0.664	0.87	[0.45, 1.67]
Val/Met[b]	-0.42 (0.29)	0.156	0.66	[0.37, 1.17]
Cardiometabolic risk score[c]	**0.76 (0.28)**	**0.007**	**2.13**	**[2.13, 3.68]**
Cardiometabolic risk score x Met/Met	**-0.87 (0.39)**	**0.025**	**0.42**	**[0.19, 0.90]**
Cardiometabolic risk score x Val/Met	**-0.83 (0.33)**	**0.012**	**0.43**	**[0.23, 0.83]**
WRAT[d]	**-0.37 (0.11)**	**0.001**	**0.69**	**[0.55, 0.86]**
Nadir CD4[e]	**-0.13 (0.03)**	**0.017**	**0.88**	**[0.79, 0.98]**
Detectable plasma viral load	**0.59 (0.29)**	**0.040**	**1.80**	**[1.03, 3.16]**
Current CD4[e]	0.03 (0.05)	0.338	1.05	[0.95, 1.11]
ARV status never used	-0.26 (0.47)	0.574	0.77	[0.31, 1.93]
ARV status past use[f]	0.15 (0.44)	0.736	1.16	[0.49, 2.72]
Non-Hispanic Black[g]	-0.37 (0.44)	0.398	0.69	[0.29, 1.63]
Hispanic[h]	0.30 (0.34)	0.374	1.36	[0.69, 2.64]

Note. Bolded predictors are significant at $p<.05$. ARV= antiretroviral therapy; OR= odds ratio; WRAT= Wide Range Achievement Test

[a]Interaction terms reflect odds rate ratios

[b]Compared to Val/Val

[c]Per 1 standard deviation change

[d]Per 10-unit change

[e]Per 50-unit change;

[f]Compared to ARV status currently using

[g]Compared to non-Hispanic White

Figure 1

Figure 1. Greater cardiometabolic risk predicts neurocognitive impairment among Val/Val only

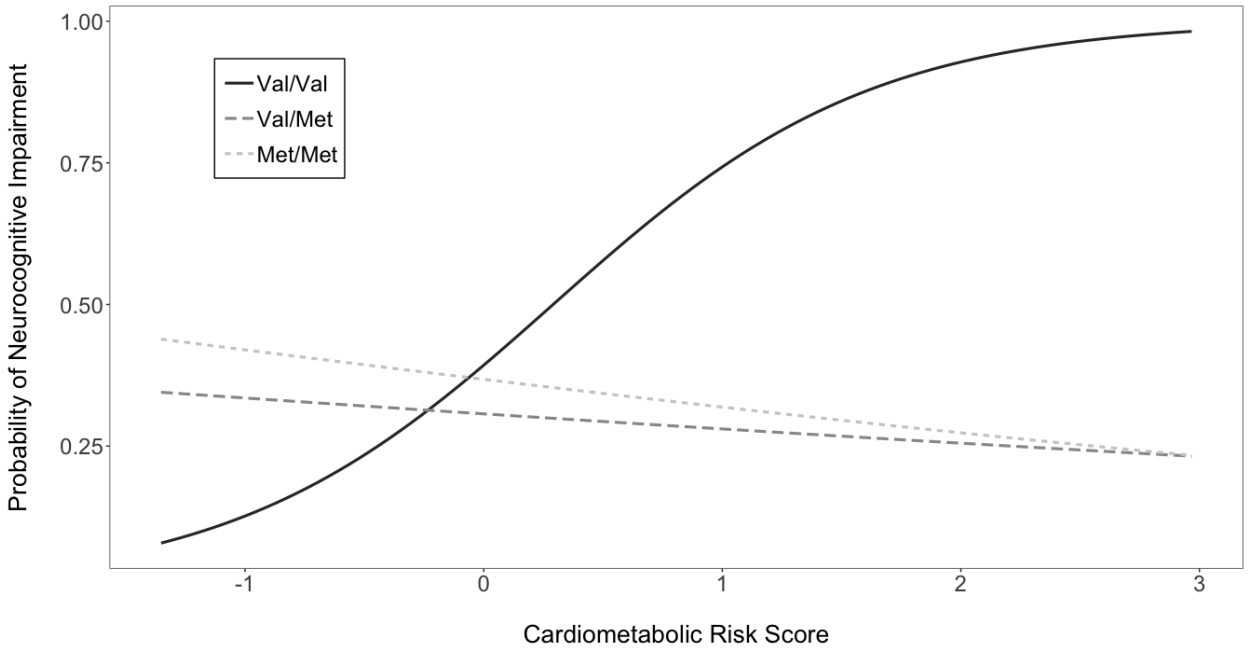

Figure 2

Figure 2. Greater cardiometabolic risk significantly increases likelihood of neurocognitive impairment in Val/Val with nadir CD4 below 180