5th International Workshop on HIV & Aging

Abstracts

Abstract: 1

Effects of HIV and Combination Antiretroviral Therapy (cART) on Cortico-Striatal Functional Connectivity

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Introduction: Combination anti-retroviral therapy (cART) has extended the lives of the HIV-infected (HIV+) yet has not eradicated cognitive impairment. Neuropsychological performance (NP) testing remains crucial for detecting neural dysfunction due to HIV. However, cognitive normality does not imply the absence of neural dysfunction, and not all individuals develop cognitive impairment. Therefore, it is important to use other modalities to detect neurological changes in the HIV-infected. Neuroimaging such as resting state functional connectivity (rs-fc) quantifies the temporal correlations of brain regions that are involved in networked communication. These resting state networks (RSN)s are well-defined regions including the default mode network (DMN) and ventral attention network (VATT). Rs-fc has proven reliable and sensitive in other diseases, including sensitivity to disease status, cognitive test performance and drug treatments. Previous pathological and magnetic resonance imaging (MRI) studies have shown HIV has a strong predilection for subcortical areas, yet functional connectivity to subcortical areas remain unknown. In this study, we determine whether HIV and cART affects rs-fc between the striatum and canonical cortical RSNs.

Methods: 49 HIV uninfected (HIV–) and 132 HIV+ (65% receiving cART) had laboratory studies (current and nadir CD4 T-cell counts, and plasma HIV viral load), NP testing, and neuroimaging. All subjects consented as approved by the Institutional Review Board (IRB) at Washington University in St. Louis. A pair of blood oxygen level dependent (BOLD) MRI scans were used to calculate Rs-fc. Rs-fc examines the coordination of neural activity in distant brain regions and was used to investigate cortico-striatal functional connections. The effect of cART was assessed comparing HIV+ individuals on cART(HIV+/cART+), and HIV+ individuals naïve to cART (HIV+/cART–). Relationships between laboratory tests, cognitive performance and cART on subcortical-cortical rs-fc were assessed by an analysis of variance.

Results: HIV+ individuals had lower cortico-striatal functional connectivity than HIV– controls, specifically between the striatum and default mode network (DMN; p <0.001) and ventral attention network (VATT; p <0.001). HIV+/cART+ individuals had higher functional connectivity between the striatum and DMN (p=0.024) and VATT (p = 0.01) compared to HIV+/cART– subjects. Laboratory (current and nadir CD4 T-cell counts, plasma viral load) and NP were not correlated with cortico-striatal functional connectivity.

Conclusions: HIV was associated with disrupted cortico-striatal networks, consistent with HIV's known impact on subcortical areas. Interestingly, HIV+/cART+ individuals had rs-fc more similar to controls, suggesting possible improvements in HIV related neural dysfunction due to medications. Rsfc may be a sensitive biomarker of neural insult and recovery following the initiation of cART.

No conflict of interest

Abstract: 2

Iron-Regulatory Genes are Associated with Aging-Related Neuroimaging Traits in HIV-Infected Persons: a CHARTER Study

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Background: HIV-Associated Neurocognitive Disorders (HAND) remain distressingly common, despite viral suppression with combination antiretroviral therapy. Structural and metabolic changes in the brain may occur early in HIV-infection and represent important endophenotypes of HAND. Brain iron dysmetabolism is a common feature of aging-related neurocognitive disorders, which also involve increases in abnormal white matter volume. We hypothesized that variants in iron-regulatory genes are associated with neuroimaging traits, particularly those linked to aging, in HIV infection and/or HAND.

Methods: We genotyped 250 SNPs in 12 iron-related candidate genes and evaluated their associations with magnetic resonance (MR) imaging traits among 243 subjects with available neuroimaging data from the CNS HIV Antiretroviral Treatment Effects Research (CHARTER) Study. Structural MR imaging (sMRI) measurements of gray and white matter volume and MR spectroscopy (MRS) measurements of brain metabolites were made in 21 regions of interest (ROI). All MRI traits were log-transformed. Multivariable regression models were adjusted for potential confounders, including: age, scanner, ancestry (by principal components), nadir $CD4^+$ T-cell count, and HIV RNA detectability in plasma, as well as outcome-specific covariates. Analyses stratified by presence of neurocognitive impairment (Global Deficit Score, GDS<0.5 or ≥0.5), virus detectability, or comorbidities were also performed, and corrections for multiple statistical tests were applied.

Results: Of 29 SNPs that were significantly associated with structural and/or metabolic traits after correction for the 37 haplotype blocks represented, 5 SNP associations also survived the most conservative correction (for number of haplotype blocks and ROI) and demonstrated biologically plausible patterns of association: (1) In subjects with detectable HIV RNA in plasma, *TFRC* SNP rs17091382 (A allele) was associated with decreased subcortical gray matter volume (adjusted *beta* coefficient (β)= -0.098, *p*=3.23e-5); (2) In subjects without detectable viral RNA, *SLC40A1* SNP rs13404407 (C allele) was associated with increased abnormal white matter volume (β=0.902, *p*=2.23e-6); (3) *SLC11A1* SNP rs7576974 (T allele) was associated with increased frontal gray matter *N*-acetyl aspartate levels (β=0.040, *p*=3.62e-5), particularly in subjects without neurocognitive impairment; and (4) in subjects with contributing comorbidities, *CP* SNP rs4974389 (A allele) and *ACO2* SNP rs9611598 (A allele) were associated with increased basal ganglia choline (β=0.048, *p*=3.52e-5) and decreased subcortical gray matter volume (β= -0.316, *p*=5.94e-5), respectively.

Conclusions: Variants in genes involved in iron transport or metabolism are associated with specific, aging-related neuroimaging attributes in HIV-infected subjects, such as abnormal white matter and subcortical gray matter volumes, and with regional metabolite levels that reflect brain inflammation and neuronal integrity. Further studies are needed to replicate these findings and assess the contributions of these variants to aging-related neuropathologies in HIV infection, including HAND.

No conflict of interest

Abstract: 3

Diastolic function predicts impaired exercise capacity in older HIV-infected men

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Background: HIV-infected adults have greater risk of diastolic dysfunction and low aerobic exercise capacity. We previously reported hypertension to be independently associated with low aerobic capacity in older HIV-infected adults. Diastolic function is associated with aerobic capacity in adults without HIV but has not been investigated in older HIV-infected adults. The study objective was to investigate the correlation of diastolic function and aerobic capacity in HIV-infected men with no prior diagnosis or symptoms of coronary heart disease (CHD).

Materials & Methods: This is a cross-sectional study of HIV-infected veterans enrolled in the VACS CVD study at the Baltimore VA site, where aerobic exercise capacity was measured by gas exchange at peak exercise during graded exercise treadmill testing (VO_2peak). Diastolic function was assessed using resting Doppler echocardiography to record early diastolic (E) and atrial (A) mitral inflow velocities as well as mitral annular longitudinal diastolic velocity (e'). Uncontrolled hypertension was defined as resting systolic blood pressure >140mm Hg. Association of VO2peak with patient characteristics was tested by t-test and linear regression models.

Results: Treadmill and echo data were available in 101 men with a mean (SD) age of 54(6) years, 94% African American race, and median CD4 cell count of 405 cells/ml. The mean (SD) VO_2peak was 27.0 (5.7) ml/kg/min. Men with uncontrolled hypertension (n=9) had significantly lower VO2peak (mean $\pm$SE: 21.9 $\pm$ 1.8 ml/kg/min, $p<0.01$). VO2peak correlated directly with myocardial relaxation (e'; $r=0.30$, $p<0.01$); directly with LV chamber relaxation (E/A ratio; $r=0.30$, $p<0.01$), and inversely with left ventricular end diastolic pressure (E/e'; $r= -0.22$, $p= 0.045$); Results were unchanged in linear regression models adjusted for uncontrolled hypertension. The association with VO2peak remained significant for e' and E/A ratio in multivariate linear regression models with age, race, and uncontrolled hypertension (p values < 0.04).

Conclusions: Diastolic function is independently associated with aerobic exercise capacity [kao1] in older HIV-infected men without history or symptoms of CHD. These novel results provide insight into the role of diastolic function in impaired aerobic capacity in older HIV-infected adults. Further research is needed to determine whether differential pathophysiologic mechanisms exist by HIV status and age. These results will inform strategies to prevent and treat physical disability in older HIV-infected adults.

No conflict of interest

Abstract: 4

Effect of chronic pulmonary lung disease on the decline in physical function in HIV infected and uninfected veterans in the Veterans Aging Cohort Study

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Background: Age-related comorbid conditions are strongly associated with physical function in HIV-infected adults. In a cross-sectional study of participants in the Veterans Aging Cohort Study (VACS) we reported that chronic pulmonary disease was independently associated with lower self-reported physical function, which was amplified in the HIV-infected group. A small sub-study of measured function showed that decreased FEV1 was independently associated with lower ambulatory performance in only the HIV-infected participants. The objective of this longitudinal study was to investigate the effect of baseline chronic pulmonary disease on change in self-reported physical function.

Materials & Methods: We performed a longitudinal analysis of 3627 HIV-infected and 3692 uninfected patients enrolled from 2002 to 2011 in the Veterans Aging Cohort Study. Data were collected from annual questionnaires and the electronic medical record. Comorbid conditions were defined by ICD-9 codes. We defined chronic pulmonary disease as chronic obstructive pulmonary disease (bronchitis and emphysema) or asthma. Self-reported physical function was measured by the SF-12 physical composite score (PCS). Summary statistics compared physical function, common medical comorbidities, lifestyle factors and demographic characteristics between HIV groups. A linear mixed model was used to determine the change in PCS over five-years of follow-up.

Results: The mean age was similar in HIV groups, 49.2 years-old (HIV-infected) and 50.5 years-old (uninfected), and 94% were male. There was no significant difference in baseline mean (SE) PCS between HIV-infected participants (43.6 (10.8)) and uninfected participants (42.3 (11.4)). HIV-infected participants were more likely to be current smokers (53%) than uninfected participants (46%). Advanced age, current smoking, and chronic pulmonary disease independently predicted a decline in the PCS ($p<0.001$). The decline in function among those with chronic pulmonary disease was not significantly different by HIV group ($\beta_{HIV*admpul}= -1.53$, $p=0.07$). After five years of follow-up, 50 year old male smokers at baseline had an estimated mean (SE) PCS of 31.1 (2.3) if HIV-infected and 31.5 (2.2) if uninfected, based on a model including demographic characteristics and baseline comorbidities and lifestyle factors.

Conclusions: This study presents novel findings on change in self-reported physical function in a cohort of HIV-infected and uninfected patients. Our results show that advanced age, current smoking, and chronic pulmonary disease independently predict a decline in physical function in both HIV-infected and uninfected patients, controlling for demographic characteristics and baseline comorbidities and lifestyle factors. In contrast to cross-sectional studies, there appears to be no differential effect of chronic pulmonary disease on physical function over time. Future research is needed with objective measures of physical function and further consideration for the effect of depression and other mental illness on self-reported physical function.

No conflict of interest

Abstract: 5

The HIV proteins tat and nef promote human bone marrow mesenchymal stem cell senescence and alter osteoblastic differentiation

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Introduction/Background: HIV-infected patients ART-naive often present a decreased bone mineral density (BMD), and a higher prevalence of osteopenia and osteoporosis. The initiation of ART induces an additional decline in BMD, and an increased bone turnover. Proposed pathogenic candidates include HIV infection and the drug regimen itself. Yet, the mechanisms involved are unknown. Bone mass turnover is maintained by the coordinated balance between bone formation by osteoblasts and bone resorption by osteoclasts. To maintain normal bone turn over, bone marrow (BM) mesenchymal stem cells (MSCs) are constantly recruited and subsequently differentiated into osteoblasts. HIV proteins are released by infected cells within BM and can impact on neighboring bystander cells. In this study, we hypothesized that the HIV proteins Tat and Nef could induce premature aging of BM-MSCs, and reduce their capacity to differentiate into osteoblasts.

Material & Methods: We compared the chronic effect (20 days) of Tat and Nef (40 ng/mL) on BM-MSCs proliferation, senescence, oxidative stress, mitochondrial dysfunctions, inflammation and autophagy. The differentiation potential of the MSCs toward the osteoblastic lineage was then assessed after 20 days pre-exposition to the HIV-proteins.

Results: When compared to non-treated cells, BM-MSCs chronically treated with Tat and/or Nef progressively reduced their proliferative activity from day 5 to day 20, and underwent early senescence from day-10. Senescence was characterized by increased pH6 beta-galactosidase activity, lysosome accumulation and the expression of cell cycle arrest protein p21. By day 20, Tat- and Nef- treated cells displayed an increase in oxidative stress and mitochondrial dysfunctions. Tat and Nef added together had cumulative effects. The addition of N-acetyl-cysteine, an antioxidant molecule, partly prevented Tat- but not Nef-induced senescence. Moreover, Tat but not Nef induced an early increase in NF-κB activity, IL-6 and IL-8 secretions. All Tat-induced effects could be prevented when cells were co-treated with parthenolide, an NF-κB inhibitor. This result indicates that Tat may trigger senescence via NF-κB activation, which could then lead to increased inflammation, oxidative stress and mitochondrial dysfunctions. Otherwise, by day 10, Nef-treatment led to the inhibition of autophagy, a lysosome-dependent cellular catabolic process, as shown by decreased LC3II/I ratio. This effect is thought to be through a direct interaction between Nef and Beclin-1 as the two proteins co-immunoprecipitated. In Nef-treated BM-MSCs, rapamycin, an autophagy inducer, could prevent Nef-induced senescence, oxidative stress, and mitochondrial dysfunctions. Finally, we evaluated the impact of HIV proteins pre-treatment on the capacity of BM-MSCs to differentiate towards the osteoblastic lineage. We showed, that Tat and/or Nef decreased calcium deposition, osteocalcin secretion and Runx2 protein expression in BM-MSCs submitted to osteoblastic differentiation.

Conclusions: In conclusion, our in vitro data show that Tat and Nef could reduce the number of available osteoblast precursors, and osteoblast differentiation by inducing BM-MSC senescence, through either enhanced inflammation or reduced autophagy. These results offer new insights into the pathophysiological mechanisms of decreased BMD in HIV-infected patients.

Part of the data were presented in the20th Conference on Retroviruses and Opportunistic Infections, Atlanta, 2013, and in the 14th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV, Washington DC, 2012.

No conflict of interest

Abstract: 6

Comparative Analysis of Macrophage Populations and their Contributions to Pulmonary Pathogenesis in Young and Aged SIV-Infected Rhesus Macaques

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Background: Pulmonary disease is a serious manifestation in AIDS patients and in older non-HIV-infected individuals, as well. Functional declines in alveolar macrophages (AM) were reported with increasing age in mice and humans that were associated with weakening of host pulmonary defense and increased pulmonary inflammation. In addition, the population of persons with HIV is growing older. Therefore, this study was designed to compare and understand the differences between lung macrophage populations in young and older rhesus macaques prior to and during the acute stage of SIV infection to begin to learn how SIV infection pathogenesis may be exacerbated in the aging HIV-infected population.

Methods: BrdU incorporation, flow cytometry, and confocal imaging were used to determine monocyte/macrophage turnover and kinetics of lung macrophage differentiation from blood monocytes in young and older rhesus macaques prior to and after SIV infection. Differential cell counts were performed on bronchoalveolar lavage (BAL) specimens stained with Wright-Giemsa and routine histology was performed on H&E-stained lung tissue sections.

Results: There was no significant difference in lung tissue structure between young and old healthy uninfected rhesus macaques. However, there was a significant decline in the absolute number of AM in the older animals that decreased the ratio of AM to interstitial macrophage (IM) (AI ratio). The declining AI ratio during aging was confirmed by differential counting of cells recovered from bronchoalveolar lavage (BAL) as well as by flow cytometry and confocal microscopy examination of macrophage population isolated from whole lung tissue. Interestingly, the decreased AI ratio was also observed in young SIV-infected rhesus macaques. When functional properties were compared, secretion of IL12 and TNF-α ex vivo from unstimulated AM of uninfected rhesus significantly increased with age, but with increasing age, the AM were significantly less responsive following *ex vivo* LPS stimulation. Interestingly, when young and aged macaques were infected with SIV, the turnover rate of IM in the older rhesus macaque was higher than in young rhesus macaque during the acute phase.

Conclusion: These results suggest that declining pulmonary host responses in older rhesus macaques could be associated with declining number and/or function of longer-lived AM macrophages of the lung. In addition, the increasing basal level of inflammatory cytokine secretion and lower responsiveness to endotoxin by the longer-lived AM of aging rhesus macaques may influence in increasing the susceptibility to SIV infection and death of shorter-lived IM during the acute phase of SIV infection.

No conflict of interest

Abstract: 7

Characterization of peripheral B cells in aged individuals

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Background: Although it has been well established aged individuals exhibit an impaired humoral response, an exhaustive characterization from aged subjects has not been undertaken. We hypothesize that the mechanisms underlying the impaired humoral response in aged individuals is multifactorial including perturbations in B-cell subsets, and dysregulated inhibitory, co-stimulatory, and Toll-like receptor (TLR) expression/signaling on B cells. In this study we have performed a comprehensive phenotypic characterization of peripheral B cells in young and aged subjects investigating the multifactorial mechanisms potentially contributing to the dysregulation of B-cell response with age.

Materials and Methods: This study analyzed peripheral B cells of healthy young and aged individuals ages 22-45 years and 65-90, respectively. Subjects were reported to be in good health by clinical staff and were not prescribed any immunomodulatory medication. We investigated the frequency of B-cell subsets, B-cell expression of B-cell receptor signaling inhibitory molecules, co-stimulatory molecules, and TLRs. Expression of co-stimulatory molecules CD40, CD80, CD86, and HLA-DR was assessed by flow cytometry, as were inhibitory molecules CD22, CD72, CD85j, CD305, and PD-L1. Finally, the expression of inhibitory proteins Fc receptor-like (FcRL) 1-5, and TLR1-10 were determined by RT-qPCR on sorted $CD19^+$ B cells.

Results: Compared to young subjects, we determined a significant reduction in the frequency of total $CD19^+$ B cells (p=0.0124) from aged subjects and resting memory B cells (p=0.0211) ($CD10^-CD20^+CD21^+CD27^+$). However, B cells from young and aged subjects expressed comparable levels of co-stimulatory molecules CD40, CD80, CD86, and HLA-DR. Additionally, compared to young subjects, aged subjects express significantly decreased levels of the inhibitory receptor CD72 (p=0.0258), but significantly increased levels of CD85j (p=0.0048). Similarly, B cells from aged subjects exhibited elevated levels of FcRL5 (p=0.0675). Finally, B cells from aged subjects exhibited significantly reduced levels of TLR5 (p=0.0029).

Conclusions: We present novel data suggesting that the mechanisms underlying the attenuation of B-cell responses with age are multifactorial including dysregulated TLR and inhibitory molecule expression, and perturbation in B-cell subsets.

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No conflict of interest

Abstract: 8

Longitudinal changes in free testosterone among older HIV-infected ans HIV-uninfected men

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Background: In the general population, aging is associated with lower testosterone levels and a decrease in the diurnal variation of testosterone secretion. Although cross-sectional studies have shown lower than expected testosterone levels in HIV-infected men, it is unclear whether age-related longitudinal changes in serum testosterone differ by HIV serostatus.

Methods: We identified HIV-infected men from the Multicenter AIDS Cohort Study (MACS), age ≥ 45 years at initiation of highly active antiretroviral therapy (HAART), who had ≥ one serum sample available prior to HAART-initiation (i.e. the baseline visit) and ≥ 2 serum samples in the 10 years following HAART-initiation. They were matched to HIV-uninfected men by age, race, MACS site and calendar time of pre and post-HAART samples. Men reporting exogenous hormones of any kind and/or had free testosterone concentrations (FT) >150 ng/dL, suggestive of unreported testosterone use, were excluded. Linear mixed effects regression was used to determine whether log FT and its rate of change over the study interval differed by HIV serostatus.

Results: Data were available from 182 HIV-infected and 267 HIV-uninfected men. The median age at baseline was 48.8 years (Interquartile range (IQR); 45.8, 53.4). The median number of FT measurements per participant was 4 (IQR; 3, 5) drawn over a median of 6 years (IQR; 2.9, 9.5). Of the 1737 samples analyzed, 65% were drawn in the morning. After adjustment for age, race, BMI, hepatitis C status, smoking, the presence of diabetes mellitus and MACS site, median baseline FT levels were significantly lower among HIV-infected men than HIV-uninfected men in morning samples (67 ng/dL [95% Confidence Interval (CI):65-71] v. 72 ng/dL [95% CI: 69-74], respectively; p=0.037), but not in afternoon/evening samples (65 ng/dL [95% CI:62-69] v. 65 ng/dL [95% CI: 62-67], respectively; p= 0.728). However, the annual rate of FT decline after adjustment for time of day of the sample draw and other covariates did not differ significantly by HIV serostatus: -1.1% for HIV- infected men (95% CI: -0.4% , -1.8%) v. -1.0% for HIV-uninfected men (95% CI: -0.6%, -1.5%), p = 0.913.

Conclusions: FT decreased similarly over a 6-year interval in older HIV-infected and HIV-uninfected men, but morning FT levels were lower among HIV-infected men, but not afternoon/evening levels. These data may suggest a loss of diurnal variation in FT among HIV-infected men.

No conflict of interest

Abstract: 9

Lower frailty index is associated with successful cognitive aging among HIV-positive adults age 50 and older

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Introduction/Background: Physiologic aging can be characterized by the number of health deficits (e.g. signs, symptoms, laboratory abnormalities, or disabilities) individuals accumulate. These can be summarized in a frailty index (FI), which is the proportion of deficits present in individuals out of 30 or more health variables. As such, the FI enables a grading of frailty among individuals, from fittest to frailest, and can be more informative in health risk prediction and stratification than the presence or absence of individual disorders. Higher FI scores have been associated with neurocognitive impairment in the general population, but such associations have not been investigated in the HIV setting, nor has an emphasis been placed on using the FI in relation to successful cognitive aging (SCA). In this study we aimed to understand associations between fitness, as measured by a lower FI, and SCA in a sample of older HIV+ adults.

Material & Methods: Consecutive HIV+ patients age 50 and older from the Modena HIV Metabolic Clinic in 2013 were invited to participate. Inclusion criteria included being on HAART for at least 1 year with suppressed HIV-RNA viral load, and not having acute psychotic disorders, severe neurological disease or end-stage organ failure that could affect neurocognition. SCA was operationalized as the absence of neurocognitive disorder or depression on neuropsychological assessment. Frailty was measured using an FI comprised of 37 health variables, which did not include markers of HIV disease severity, immune deficiency, HIV-associated non-AIDS (HANA) condition diagnoses, or cognitive impairment. An FI was calculated as the proportion of deficits out of the total number of variables. Theoretically, scores can range from 0 (least frail) to 1 (most frail). The presence of eight HANA conditions (cardiovascular disease, hypertension, diabetes, liver cirrhosis, chronic obstructive pulmonary disease, osteoporosis, and cancer) were also assessed. Multimorbidity was defined as the presence of $\geq$2 HANA conditions. Cross-sectional multivariate logistic regression models adjusted for age (years) and gender were used to assess the odds of SCA: first, in relation to each of the HANA conditions (in separate models), second, in relation to multimorbidity, and third, in relation to the FI (0.1 increments).

Results: 103 participants aged 50 and older were included in the analysis (mean age 56.4 ± 6.1 years, 27% female). 39% of the sample was identified as experiencing SCA. After adjustment for age and gender, SCA was not associated with any of the individual HANA conditions, or with multimorbidity. FI was significantly associated with SCA (OR=0.64, CI=0.41-0.97 p=0.04). That is, for each 0.1 decrease in FI score, the odds of SCA increased by 36%.

Conclusions: The FI can be useful in grading levels of frailty and provides more information than that of individual age-related disease diagnoses or chronological age. Among this sample of older adults living with HIV, low frailty was associated with successful cognitive aging. Considering health status and frailty in a more holistic sense may be useful in the understanding of successful cognitive aging among people living and aging with HIV.

No conflict of interest

Abstract: 10

Frailty and age are independently associated with patterns of HIV antiretroviral use in a clinical setting

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Background: Guidelines recommend anti-retroviral (ARV) regimens according to viral rebound, immune depletion, or clinical sequelae. However among HIV-positive persons with undetectable viral load and satisfactory immune status, clinicians might make prescribing decisions based on other factors, including impressions regarding overall health (i.e. frailty), age, or gender. We sought to describe patterns of ARV use in relation to these factors in a clinical setting.

Materials & Methods: We retrospectively reviewed 1240 participants' data from the Modena HIV Metabolic Clinic cohort, providing 5024 annual study visits (2008-2014) when ARV regimen was considered. Observations with undetectable viral load and CD4≥500 were included. Frailty was quantified via 37-item frailty index (FI), based on the cumulative deficits model. FI variables excluded markers of HIV severity or immune depletion. FI was calculated as the proportion of health deficits present, and retrospectively assigned for each visit. ARV regimens included 2NRTI backbones plus either: PI; integrase inhibitor (RAL, only raltegravir was available), or NNRTI. We separately identified NRTI-sparing regimens.
We compared prevalence of ARV regimens in relation to frailty across 0.1 FI increments, from fit to frail, using Kruskall-Wallis tests. Multivariable logistic regression models provided odds of each regimen based on FI (0.1 increments), age (years), gender, and nadir CD4 (<100; 101-350; 351-500; >500). We then identified participants who were concurrently in both the frailest and oldest quartiles (median age 57; median FI 0.41), and compared their regimens to those of all other participants (median age 47; median FI 0.27).
In sensitivity analyses we repeated these investigations using participants' most recent visit as the unit of analysis.

Results: PI use increased with frailty severity (FI<0.1=42%; 0.1-0.19=49%; 0.2-0.29=61%; 0.3-0.39=68%; ³0.4=74%, p<0.001), while RAL use increased non-significantly (8%; 13%; 14%; 12%; 15%, p=0.2). Frailer participants less often used NNRTI (51%; 57%; 48%; 45%; 42%, p<0.001) or NRTI-sparing regimens (18%; 10%; 10%; 7%; 7%, p<0.001). In multivariate models, odds of PI use increased starting from FI ≥0.2 (e.g. FI 0.2-0.29, OR=1.97, 95% confidence interval 1.33-2.93) and decreased with higher nadir CD4 (OR=0.74, 0.66-0.83), but were unassociated with age or gender. RAL use increased with age (OR=1.04, 1.02-1.05) and nadir CD4, but was unassociated with frailty or gender. NNRTI use decreased with age (OR=0.98, 0.97-0.99) and female gender, but was unassociated with frailty or nadir CD4. NRTI-sparing regimens were significantly less common with FI ≥0.1 (e.g. FI 0.1-0.19, OR=0.49, 0.28-0.84) but more common with age (OR=1.02, 1.00-1.03) and higher nadir CD4. Participants in the frailest and oldest quartile more often used PI (70% vs. 61%, p=0.001), and RAL (17% vs. 13%, p=0.1), and less often used NNRTI (38% vs. 49%, p<0.001), than other participants. Participants' most recent study visit showed similar distributions in ARV prevalence in relation to frailty, and the same predictors were identified in multivariable regressions.

Conclusions: Differences in ARV regimens were observed in relation to frailty, age, and gender; RAL seems the most versatile with regards to age and frailty severity. This may depict a clinical attitude towards ARV selection that incorporates other factors, including judgments about frailty status.

No conflict of interest

Abstract: 11

Exploring aging trajectories among people with HIV and a general community-based cohort: transitions in health status and risk of death

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Background: Aging can be characterized by the number of deficits in health (e.g. signs, symptoms, laboratory abnormalities) individuals accumulate, and assessing longitudinal trajectories of deficit accumulation can provide insight into aging processes. In this study we aimed to apply a multistate model of health transitions within two Italian cohorts: a community-based general population cohort, and a HIV clinical cohort. We examined transitions in deficit counts and risk of death within each cohort in relation to baseline health deficits, age, and gender.

Materials & Methods: Secondary analysis of data from the Italian subsample of the Survey of Health, Ageing, and Retirement in Europe (SHARE) and the Modena HIV Metabolic Clinic (MHMC) cohort. SHARE participants (n=2,500; mean age 64±9, range 39-100 years, 56% women) were community-dwelling people age ≥50 years and their spouses, surveyed biennially. MHMC participants (n=2,817; mean age 46±8, range 16-76 years; 32% women) visited annually. Following the cumulative deficits/frailty index approach, each participant's health state was quantified as the number of health deficits out of 31 variables selected separately in each cohort. Probabilities of health state changes, including death, were evaluated over 4-year intervals using a multistate transition model. First we assessed the relationship between deficit count at baseline and average deficit count at follow-up. Probabilities of deficit counts at follow-up and risk of death were then assessed in relation to baseline deficit count, age, and gender, with multivariable Poisson and logistic regression models, respectively.

Results: Average deficit count after 4 years showed linear relationships with deficit count at baseline (SHARE: $y=1.93+0.74x$, $R^2=0.94$; MHMC: $y=2.95+0.61x$, $R^2=0.97$). Health status (deficit counts) generally worsened with age. For example, participants with 3 deficits at baseline in SHARE increased to mean 3.84±2.80 and in MHMC increased to mean 4.07±1.94. Stability and improvement in health over time were also observed in both cohorts, though MHMC participants were more likely to worsen (accumulate deficits) than SHARE participants. For example, among participants with 3 deficits at baseline: in SHARE, 55% worsened, 54% were stable or improved, and 1% died; while in MHMC, 92% worsened, 8% were stable or improved, and 0 died. In SHARE, significant predictors of deficit count at follow-up were baseline deficit count (β=0.08), age (β=0.01), and female gender (β=0.10; all $p<0.001$). In MHMC, significant predictors of deficit count at follow-up were baseline deficit count (β=0.08; $p<0.001$) and age (β=0.01; $p=0.002$), but not gender ($p=0.1$). At 4 years follow-up, 4% of SHARE participants and 1% of the MHMC participants had died. Significant predictors of mortality risk in SHARE were baseline deficit count (β=0.13, OR 1.14, 95% CI 1.10-1.18), age (β=0.09, OR 1.10, 1.07-1.12), and female gender (β=-0.79; OR 0.45, 0.29-0.70; all $p<0.001$). In MHMC, baseline deficit count (β=0.26; OR=1.30, 1.15-1.48; $p<0.001$) was a significant predictor, while age and gender were not (both $p>0.05$).

Conclusions: We observed reproducible characteristics in the dynamics of health transitions between cohorts. People in the HIV clinical cohort were more likely to experience worsening health status, i.e. accumulate more deficits, after four years, yet exhibited less variability in their outcomes.

No conflict of interest

Abstract: 12

Accelerated Longitudinal Gait Speed Decline in HIV-Infected Older Adults

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Background: Although life expectancy with HIV has been considerably extended, whether HIV affects health span and active life expectancy remains undefined. Gait speed predicts functional decline, disability, and death and is considered a biomarker of biological aging. Thus, assessment of gait speed in persons aging with HIV may provide an important method of gauging health and potential longevity in this population.

Materials & Methods: The study was performed between 2007 and 2013 in the Multicenter AIDS Cohort Study (MACS). Usual gait speed was assessed in 1,615 (749 HIV+ and 866 HIV-) men ≥40 years (mean baseline age 50.2 ± 7.6 years) and modeled using generalized estimating equations adjusted for HIV serostatus, age, race, education, smoking, drug and alcohol use, diabetes, kidney disease, liver disease, hypertension, arthritis, depression, hepatitis B, and hepatitis C. The primary outcome was usual gait speed in meters per second (m/s) and slowed gait was defined as gait speed less than 1.0 m/s. In HIV-stratified models, coefficients were included for nadir CD4, viral load, history of AIDS, and time on highly active antiretroviral therapy (HAART).

Results: Usual gait speed at age 50 averaged 1.24 m/s and 1.19 m/s for HIV- and HIV+ men, respectively ($p<0.001$). In adjusted models, gait speed declined with each one-year increase in age between ages 50 and 65 ($\beta=-0.003$, $p=0.028$), with a steeper decline after age 65 ($\beta=-0.008$, $p<0.001$). There was a negative association between gait speed and HIV status ($\beta=-0.018$, $p=0.049$) and a significant interaction between HIV and age ($\beta=-0.002$, $p=0.001$), indicating those with HIV tended to walk slower over time. There was a 77% greater risk of developing clinically slow gait (<1.0 m/s) in HIV+ compared with HIV- men (aHR 1.77; 95% CI, 1.34 – 2.33). Among those with HIV, the proportion of time on HAART was strongly associated with slower gait speed ($\beta=-0.141$, $p<0.001$), independent of nadir CD4, viral load, and history of AIDS ($p>0.05$ for all).

Conclusions: Findings of a significant difference in the rate of gait speed decline by HIV-status support the hypothesis that HIV-infected individuals may have a greater risk of future mobility limitations and disability than similar HIV-uninfected persons. When considered in conjunction with the increased risk of comorbidities that has been noted in this population, there is considerable concern that a new type of HIV-epidemic may be on the horizon; one characterized by an expansion of morbidity and disability among those aging with HIV. Accordingly, clinicians should consider screening HIV-infected patients over the age of 50 for clinical dismobility and new interventions should be established to prevent mobility disability in HIV-infected older adults.

Conflict of interest: JA Schrack was funded in part by a 2014 developmental grant from the Johns Hopkins University Center for AIDS Research, an NIH funded program (1P30AI094189), which is supported by the following NIH Co-Funding and Participating Institutes and Centers: NIAID, NCI, NICHD, NHLBI, NIDA, NIMH,NIA, FIC, NIGMS, NIDDK, and OAR.

Abstract: 13

Quality of Life and Self-Reported Lower Extremity Function in Adults with HIV-related Distal Sensory Polyneuropathy

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Background: Distal sensory polyneuropathy (DSP) is a common complication of HIV disease. Its effects on quality of life and function have not been well described. This study's aims were to compare QOL and lower extremity function in HIV+ individuals with or without DSP, determine the extent to which function predicts QOL, evaluate agreement of two function scales, and describe utilization of pain management resources.

Materials & Methods: We conducted a cross-sectional survey study of quality of life and self-reported lower limb function and used predictive modeling to determine the relationship between function and quality of life. In addition, we assessed concordant validity of 2 self-report outcome tools for lower extremity function. Materials included a demographic questionnaire, the MOS-HIV, the Lower Extremity Functional Scale (LEFS), Lower Limb Functional Index (LLFI), and review of medical records. A general linear model was used to assess group differences on QOL and the relationship between function and QOL. Bland-Altman procedures were used to assess the agreement of the LEFS and LLFI. Chi-square tests were used to determine differences in utilization of pain management resources.

Results: Of the 94 participants enrolled, 82 had usable data for analyses. The 67% who reported DSP symptoms tended to be older (p=0.011), had HIV longer (p=.039) and were more likely to receive disability benefits (p=.014). Participants without DSP had better LLFI and LEFS scores, and better MOS-HIV Physical Health Summary scores (p<0.001) compared to those with DSP. In multivariate models, lower limb function significantly predicted physical and mental health scores. The LLFI was found to identify individuals with lower function more often than the LEFS. Individuals with DSP were more likely to utilize medical treatment (p<0.001), physical therapy (p=0.002) and complementary or alternative treatments (p<0.001) compared to those without DSP.

Conclusions: In individuals with HIV disease, QOL and self-reported lower limb function are more impaired in those with DSP than those without DSP. The LLFI was more likely to capture limitation in function than the LEFS. Patients with DSP reported more frequent use of pain management resources.

Disclosure: Article based on this work has been accepted and is in press with Physical Therapy (tentatively slated for print version fall 2014).
PTJ has granted us permission to present this work.

Abstract: 14

Premature Aging in HIV+ or Premature Conclusions? A Systematic Review and Meta-analysis

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Background: Premature aging in HIV-infected adults is contentiously debated. We systematically reviewed the literature for studies reporting two metrics: differences in age distribution of, and risk of, end-stage renal disease (ESRD) and myocardial infarction (MI).

Material & Methods: We searched MEDLINE and EMBASE databases through August 2011 using combinations of controlled vocabulary and free text words without language restriction. Two authors independently reviewed titles and abstracts and then full text reports for studies that: 1) reported outcome of interest; 2) included an HIV- comparison group; 3) used a design that was not a review article, case study, or case series. Discrepancies were adjudicated by consulting a 3rd reviewer. We meta-analyzed the relative risks for ESRD and MI studies using DerSimonian-Laired random effects models.

Results: After removing duplicates, 2,246 ESRD and 1,798 MI cancer titles and abstracts were reviewed, from which 24, and 46 articles were reviewed in full, respectively. After excluding studies that did not report an age at diagnosis or a relative risk of outcome by HIV status, we included 2 ESRD and 12 MI studies. No studies reported age at ESRD diagnosis. The pooled estimate of ESRD in HIV+ compared to HIV- was 6.10 (5.89, 6.30, p-value for heterogeneity = 0.558)). Both studies adjusted for age and race, but the study populations were predominantly black. Four MI studies reported age at diagnosis. HIV- were ≥10 years older than HIV+ at MI diagnosis. All four studies concluded that the age at MI diagnosis was younger in HIV+ compared to HIV-, but the younger age distribution of HIV+ compared to HIV- was not mentioned. Of the 8 MI studies that compared MI risk in HIV+ with HIV-, the pooled relative risk was 1.87 (1.63, 2.14, p-value for heterogeneity = 0.078). Only 1 MI study adjusted for smoking status.

Conclusions: There is a lack of evidence showing a younger age at diagnosis of ESRD and MI. We found many examples of over-interpretation of the difference in age at MI diagnosis. While evidence of excess risk for these conditions among HIV+ compared to HIV- is compelling, differentiating between earlier age at diagnosis and risk of disease is essential to understanding the aging process in HIV-infected adults. Updates for these two outcomes, and similar reviews and meta-analyses among HIV- and HIV+ adults with cancer and frailty outcomes are nearing completion.

No conflict of interest

Abstract: 15

Prevalence and Correlates of Research-Defined Successful Aging Among Older HIV+ Adults

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Background: Although the prevalence and incidence of HIV among older adults is increasing, data are limited regarding the proportion of older HIV-infected (HIV+) persons who are aging successfully, as well as the factors that may contribute to successful aging (SA). In particular, positive psychological factors such as optimism and resilience have been shown to facilitate SA among non-HIV infected older adults (HIV-) and such factors may inform intervention strategies to promote SA in older HIV+ adults. Definitions of SA vary and recent research suggests that SA definitions that include freedom from physical disease or disability are overly restrictive, particularly among persons living with chronic diseases such as HIV. The purpose of the current study was to: 1) estimate the proportion of older HIV+ and HIV- adults who meet a research-defined phenotype of SA (i.e., freedom from cognitive, everyday functioning, and emotional impairment); 2) compare subjective self-rated SA across HIV/SA groups; 3) compare several psychological factors and health-related quality of life across the HIV/SA groups.

Materials & Methods: Cross-sectional data from 100 HIV+ and 48 HIV- older adults (i.e., ≥ 50 years old) were examined. SA was defined as freedom from: 1) neurocognitive impairment (assessed with a comprehensive, seven-domain, neurocognitive battery using normative standards), 2) current major depressive disorder diagnosis (determined via structured clinical interview), and 3) dependence in performance of instrumental activities of daily living (IADLs; determined via Lawton and Brody questionnaire, in which decline/need for assistance in two or more IADL domains was reported). Participants also completed several questionnaires of psychological traits, health-related quality of life, and a single self-rated SA question (measured on a 10-point Likert-type scale with 1 being the least successful and 10 being the most successful).

Results: Thirty-nine percent of the HIV+ sample met research-defined SA criteria as compared to 56% in the HIV- sample (p=0.04). When examining the four resulting groups (all combinations of HIV and SA) pairwise tests showed that the HIV+ non-SA group had the lowest self-rated SA score as compared to the other three groups, which did not differ from one another. Similarly, on several psychological trait questionnaires (e.g., optimism, resilience, life satisfaction, social support, perceived stress) and health-related quality of life, HIV+ non-SA participants had significantly (ps < 0.05) poorer scores than HIV+ SA, HIV- SA, and HIV- non-SA groups.

Conclusions: Over a third of older HIV+ subjects meet research-defined criteria for SA; however, this proportion was less than that found among HIV- adults of comparable age. Several positive psychological traits were correlated with SA, and the direction of the associations suggests that these traits may be particularly protective for HIV+ subjects. Future research is warranted with HIV+ persons of all ages to both better understand the predictors of SA and to determine if interventions to achieve SA are possible.

No conflict of interest

Abstract: 16

The Influence of HIV Infection on Non-infectious Comorbidities in an Aging Cohort

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Background: With the advent of more effective antiretroviral therapy (ART), HIV-infected patients are living longer. Various studies have suggested that non-infectious comorbidities (NICMs) are more frequent and occur earlier in the course of HIV infection. We compared the prevalence of NICMs in HIV-positive and HIV-negative patients attending clinics in an urban institution.

Methods: A retrospective chart review from April 1, 2011 through March 1, 2013 of 1253 patients aged 60 years and older was conducted. One hundred HIV-positive and 1153 HIV-negative patients received their care at the HIV Program and the Adult Medicine Office, respectively. Demographic data (age, gender, and race) and the presence of NICMs including coronary artery disease (CAD), hypertension (HTN), chronic kidney disease (CKD), diabetes (DM), hyperlipidemia, malignancies, depression, and other psychiatric diagnoses were assessed. The frequency of NICMs was analyzed using univariate chi-square. Logistic regression, adjusted for NICMs and stratified by CKD as a potential confounder, was used to determine the association between HIV status and CAD.

Results: There were one hundred HIV-positive and 1153 HIV-negative patients with a mean age of 65.8 and 68.4 years, respectively. Of the HIV-positive group, 58% were male and 78% were African-American; in the HIV-negative group 39% were male and 53% were African-American. The frequency of NICMs was as follows for HIV-positive and HIV-negative patients, respectively: CAD 24% and 16% (p=0.038), HTN 66% and 81% (p<0.001), hyperlipidemia 62% and 68% (p=0.219), DM 33% and 34% (p=0.813), CKD 36% and 7% (p<0.001), malignancy 20% and 12% (p=0.026), depression 32% and 22% (p=0.021), and other psychiatric diagnoses 27% and 17% (p=0.016).
In those without significant CKD (CKD stages 1 and 2) increasing age (OR 1.024, 95% CI 1.001 – 1.05, p = 0.04), hypertension (OR 2.70, 95% CI 1.49 – 4.90, p = 0.001), and hyperlipidemia (OR 2.94, 95% CI 1.83 – 4.70, p < 0.0001) were associated with increased risk of CAD. The presence of HIV had no significant association with CKD risk in this strata (OR 1.21, 95% CI 0.57 – 2.55, p = 0.62). However, in those with CKD stage 3 or higher the presence of HIV was associated with almost 3 times the risk of CAD (OR 2.89, 95% CI 1.06 – 7.91, p = 0.038). Female sex was associated with reduced risk in both populations (CKD 1-2: OR 0.45, 95% CI 0.32 – 0.64, p < 0.0001; CKD 3-5: OR 0.28, 95% CI 0.12 – 0.67, p = 0.004). No other factors in those with advanced CKD were found to be significantly associated with CAD.

Conclusions: Our results indicate that CAD, CKD, malignancies, depression, and other psychiatric illnesses occur more frequently in HIV-positive patients. These results are similar to other studies previously reported in the literature. However, hypertension occurred more frequently in HIV-negative patients and there was no difference in diabetes and hyperlipidemia between groups. Interestingly, HIV appeared to be a risk factor for CAD only in the presence of CKD. Additional research is needed to identify the role of HIV infection and its impact on NICMs.

No conflict of interest

Abstract: 17

Switching to Stribild from a RTV-boosted PI or NNRTI with TVD Maintains HIV Suppression at Week 48 with No New Safety Signals in Subjects Age ≥50 years

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Background: In the STRATEGY(S)-PI and STRATEGY(S)-NNRTI studies, switching to Stribild (STB) from a ritonavir-boosted protease inhibitor (PI + RTV) or non-nucleoside reverse transcriptase inhibitor (NNRTI) with emtricitabine and tenofovir (TVD) was virologically noninferior (STB statistically superior over PIs) at week 48 with no new safety signals. Based on a special population sub-analysis, we report the safety and efficacy of STB in subjects age ≥50 years through week 48 from these studies.

Material & Methods: Virologically suppressed (HIV RNA < 50 copies/mL for ≥6 months) HIV-infected subjects were randomized (2:1) to switch to STB or continue a PI + RTV or NNRTI with TVD regimen. Randomization was not stratified by age. Eligibility criteria included eGFR ≥70 mL/min, no documented resistance to FTC and TDF, and no history of virologic failure. Efficacy (proportion of subjects that maintained HIV-1 RNA <50 copies/mL by FDA snapshot algorithm at week 48) and safety analyses by age ≥50 years was a post-hoc analysis. Patient satisfaction with STB vs a PI + RTV or NNRTI-based regimen was assessed using the HIV Treatment Satisfaction questionnaire.

Results: In the S-PI study, 433 subjects were randomized, of which 18% (77) were ≥50 years old (87% male; 45% smokers, 36% had hyperlipidemia, 16% were on lipid lowering agents [LLAs] and 25% had hypertension). 54 subjects switched to STB and 23 remained on their PI + RTV regimen. In the S-NNRTI study, 434 subjects were randomized, of which 22% (96) were ≥50 years old (88% male, 42% smokers, 38% hyperlipidemia, 20% on LLAs and 36% had hypertension). 71 subjects switched to STB and 25 remained on their NNRTI regimen. At Week 48, of the subjects ≥50 years old, 96% STB vs. 86% PI + RTV and 92% STB vs 96% NNRTI maintained HIV-1 RNA <50 copies/mL by FDA snapshot algorithm. There was no emergent resistance in any group. Median CD4 cell count increases from baseline at week 48 were similar between groups. Discontinuations due to adverse events were infrequent; there were no cases of proximal renal tubulopathy in any group. As expected due to the known cobicistat-mediated inhibition of renal tubular creatinine secretion, switching to STB was associated with an early and non-progressive decline in eGFR. Median changes in the ratio of total to HDL cholesterol at week 48 were small and similar between groups (-0.3 STB vs 0 PI, p=0.23; 0.2 STB vs 0.1 NNRTI, p=0.92). Switching to STB was associated with higher treatment satisfaction scores (median score [range: -30 to 30] at week 24: 27.0 STB vs 24.0 PI, p=0.44; 27.0 STB vs. 13.5 NNRTI, p=0.010).

Conclusions: In this post hoc analysis of virologically suppressed HIV-infected subjects age ≥50 years, switching to STB from a RTV-boosted PI or NNRTI with TVD maintained high rates of virologic suppression at Week 48 with no new safety signals. STB may be a viable switch option for the aging HIV patient desiring a regimen modification or simplification.

Conflict of interest: Gilead consultant, investigator, research contractor, scientific advisor, speaker.

Abstract: 18

Circadian variation of absolute CD4 count in older healthy individuals and hiv-aids patients at Butare UniversityTeaching Hospital

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Background: Decrease in T-helper lymphocyte percent and absolute number is one of the most important immunological alterations in HIV-related disorders. Absolute CD4 counts are therefore routinely used by clinicians to initiate and monitor treatment of HIV-AIDS patients although they present circadian while CD4 percentage is being only used for children. Therefore, it is critical to analyze the variability of absolute CD4 and CD4 percentage count throughout a day in volunteers aged 50 or over.

Methods: Two Groups of volunteers aged between 50 -65 years were investigated . The first was made of 21 healthy volunteers from whom 2ml of venous EDTA blood was collected four times a day at intervals of 4 hours. In the second group of 17 HIV positive, 2ml of venous blood were collected. Blood samples were incubated 15 min with CD4 and CD45 phycoerythrin- conjugated monoclonal antibodies and analyzed for lymphocytes subsets on a flow cytometer, CyFlow Counter. (Partec, GmbH, Gorlitz, Germany).Statistical analyses were performed using wilcoxon test.

Results: The study showed significant increase of absolute CD4 count (P<,0.05)in both healthy and HIV positive individuals .Rate of increase of the absolute CD4 counts was around 13% after 4 to 6 hours. This confirmed circadian variation of lymphocytes previously observed and related to cortisol concentration in the blood stream.CD4 Percentage presented no significant increase.

Conclusions: The results confirmed that a fix sampling time should be considered for a routine absolute CD4 count for management of AIDS-patients. We suggest that CD4 percentage should be also considered for the monitoring of adults living with HIV- AIDS.

No conflict of interest

Abstract: 19

Longitudinal changes in brain functional connectivity in HIV infected subjects after commencement of anti-retroviral therapy

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Introduction: While HIV infection is known to affect inter-regional brain functional connectivity, commencement of combination antiretroviral therapy (cART) in the HIV-infected population has been associated with improvement in cognitive function. Even so, the neural mechanisms of such improvements are poorly understood.
Our study seeks to identify a physiologic basis for changes in cognitive function that occur in HIV infected individuals who are started on cART through examining longitudinal changes in brain functional connectivity using resting state functional MRI (rs-fMRI). We investigated whether: (1) resting state inter-regional functional connections are influenced by commencement of cART, and (2) whether these changes are most evident in connections involving the default mode network (DMN), a collection of brain regions thought to be involved in autobiographical or introspective processing.

Material & Methods: Nine HIV infected subjects, 22-55 years of age who were cART-naïve but ready to begin antiretroviral therapy were followed longitudinally with rs-fcMRI performed at baseline (prior to commencement of cART) and at 3 months and 6 months after initiation of therapy. Structural and functional MRI data were collected using a whole body 3T scanner (Siemens, Erlangen, Germany) with a standard quadrature transmit-receive head coil. During the resting state acquisitions, no specific cognitive tasks were performed and patients were instructed to close their eyes, relax, and remain awake. Rs-fcMRI data analysis was carried out using SPM12 and the Conn Toolbox. Preprocessing included motion correction, slice time correction, spatial normalization to MNI space, spatial smoothing, bandpass filtering (0.008-0.1 Hz), and outlier elimination. Physiological denoising was accomplished using anatomical CompCor. Inter-regional correlations were explored using seed-based correlations.

Results: A typical average inter-regional correlation structure in the DMN regions, including medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and lateral parietal cortex (LLPC and RLPC), was identified when combining the results across all three sessions for all nine subjects. Longitudinal analysis of the inter-regional correlations revealed increases in connectivity with time in the connections between MPFC and the angular gyrus and decreases in connectivity over time with the mid-cingulate gyrus. PCC exhibited decreases in connectivity with time in the inferior temporal gyrus. LLPC and RLPC exhibited decreases in connectivity with time with the inferior and middle temporal gyri.

Conclusions: While HIV infection does not appear to dramatically affect the correlations among the nodes comprising the DMN, the functional coupling of the DMN to other brain regions changes with cART treatment. After six months of cART therapy, the correlations of the principal DMN node structures with cortical areas outside the DMN weakened, consistent with a general decoupling of DMN activity with other resting state networks.

No conflict of interest

Abstract: 20

STaR: Outcomes in ART-Naïve Adults >50 Years Old for Rilpivirine/Emtricitabine/ Tenofovir DF vs Efavirenz/Emtricitabine/ Tenofovir DF through Week 96

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Background: As HIV-infected adults are living longer, it is important to understand the safety and efficacy of antiretroviral therapies in older individuals. This is the first study to directly compare the safety and efficacy of the two single-tablet regimens (STRs), rilpivirine/emtricitabine/ tenofovir DF (RPV/FTC/TDF) and efavirenz/ emtricitabine/tenofovir DF (EFV/FTC/TDF) in treatment-naïve adults.

Methods: STaR is a randomized, open-label, 96-week study to evaluate the safety and efficacy of the STR RPV/FTC/TDF compared to the STR EFV/FTC/TDF in treatment-naïve, HIV-1 infected subjects. Subjects were randomized 1:1 to RPV/FTC/TDF or EFV/FTC/TDF. Randomization was stratified by HIV-1 RNA level (≤100,000 c/mL or >100,000 c/mL) at screening. The primary endpoint was the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 using the snapshot algorithm (12% pre-specified non-inferiority margin). Here we present the post-hoc analyses of outcomes for subjects age > 50 years old (yo).

Results: A total of 786 subjects were randomized and dosed (394 RPV/FTC/TDF; 392 EFV/FTC/TDF). Baseline characteristics were similar between treatment arms. For the subpopulation of subjects >50 years old (n=43 in the RPV/FTC/TDF arm, n=47 in the EFV/FTC/TDF arm), the median age was 55 yo (range 51-74). Overall RPV/FTC/TDF was non-inferior to EFV/FTC/TDF at Week 48 (85.8% vs 81.6%; difference 4.1%, 95% CI [-1.1% to 9.2%]) and at Week 96 (77.9% vs 72.4%; difference 5.5%, 95% CI [-0.6% to 11.1%]) for HIV RNA <50 c/mL per Snapshot analysis. For subjects >50 yo, rates of virologic suppression at Week 96 were 83.7% (36/43) RPV/FTC/TDF vs 74.5% (35/47) EFV/FTC/TDF by Snapshot analysis (difference 10.5%, 95% CI: -6.7% to 27.8%, p=0.22). The incidence of virologic failure was 2/43 RPV/FTC/TDF vs 0/47 EFV/FTC/TDF. In the safety analysis of this subpopulation, the number of subjects that discontinued due to adverse events were 3/43 RPV/FTC/TDF vs 6/47 EFV/FTC/TDF. In the RPV/FTC/TDF arm, 7/43 reported Grade 3 or 4 adverse events compared to 9/47 in the EFV/FTC/TDF arm. There were similar rates of Grade 3 or 4 laboratory abnormalities in both arms (10/43 RPV/FTC/TDF vs 9/47 EFV/FTC/TDF). Median eGFR at Week 96 was 91.1 mL/min in the RPV/FTC/TDF arm and 95.5 mL/min in the EFV/FTC/TDF arm. There was little change in fasting lipids in the RPV/FTC/TDF arm through Week 96, whereas there was significantly greater worsening of total cholesterol and improvement in HDL through Week 96 in the EFV/FTC/TDF arm.

Conclusions: In the overall study population, RPV/FTC/TDF demonstrated non-inferior efficacy to EFV/FTC/TDF. In subjects >50 yo, RPV/FTC/TDF maintained similar rates of virologic suppression and failure, had fewer discontinuations due to adverse events, and similar rates of Grade 3 or 4 adverse events. There were no new renal or lipid safety concerns when using RPV/FTC/TDF in older patients.

Conflict of interest: Research Grants (by Gilead) and/or Gilead employees/stockholders

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Interruption of accelerated aging in HIV infected individuals by reducing systemic immune activation

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Introduction: HIV-infected individuals successfully treated with antiretroviral therapy (ART) do not attain normal longevity. It has been shown elevated markers of inflammation including highly sensitive C-reactive protein (hsCRP), IL-6, D-dimer, and cystatin C levels in HIV-infected patients compared to uninfected individuals. Immune activation associated with HIV infection has included increased expression of CD38, HLA-DR, Ki-67 and bcl-2 by T cells across many additional studies. The persistence of immune activation and a pro-thrombotic inflammatory state during suppressive ART has been linked to increased cardiovascular, cerebral and renal disease and is thought to result from leakiness of the gastrointestinal (GI) and genital mucosa, due to inadequate and dysregulated mucosal lymphocytes, which allows lipopolysaccharide (LPS) to leak into the systemic circulation, i.e., microbial translocation. Why the gut mucosa fails to fully recover after initiation of ART is unknown. Multiple factors could perpetuate gut injury. In conjunction with intestinal loss of regulatory T cells (Tregs) and immunosuppressive function, this cascade could maintain chronic systemic immune activation. This persistent immune activation state has been linked to accelerated aging in HIV-infected individuals.

Materials & Methods: Peripheral blood mononuclear cells (PBMC) specimens from 12 HIV sero-negative individuals were used for this study. In vitro functional assays (e.g. flow ex vivo infection assay, flow cytometry analysis, RT-PCR, T cell proliferation and immunophenotyping assays) were performed in the presence and absence of physiologically relevant levels of atorvastatin.

Results: Our results demonstrate that atorvastatin directly reduces immune activation markers such as CD38, HLADR and Ki67 on $CD8^+$ and $CD4^+$ T cells, expands Tregs, and prevents HIV replication and infection.

Conclusion: Therefore *atorvastatin* and possibly mesalazine are drugs that target the mechanisms integral to immune activation pathways, hence their interruption could *allow the gut to heal*, and thereby diminish systemic immune activation. Our data may direct us to new therapeutic options to reverse the pro-inflammatory state, and thus, benefit the health of HIV-infected individuals, including improved cardiac and cerebral function to prevent accelerated aging.

No conflict of interest

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