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Abstract Book

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Abstracts

Oral Presentations

Abstract: O_01

HIV-infected individuals display defects in baseline and inducible STAT3 phosphorylation which are associated with a low nadir CD4 T-cell count

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Background: Similarities between various immune traits in HIV and aging and increased rates of age-associated co-morbidities in HIV suggest that HIV may lead to early aging. However, there has been limited examination into the additive effects of aging and HIV on the immune system, especially with respect to their contributions to cell signaling abnormalities. In uninfected individuals, higher baseline and reduced cytokine-induced phosphorylation of STAT 1, 3, and 5 is seen with aging and is associated with reduced influenza antibody titers and other features of immune senescence. Here, we use phospho-flow to examine the influence of age on STAT signaling in HIV-infected and HIV-uninfected individuals.

Materials and Methods: We recruited 12 younger (25-40 years) and 12 older (55 years or older) virologically-suppressed HIV-infected subjects and 89 HIV-uninfected subjects (20-96 years). We obtained clinical histories from HIV-infected subjects including duration of infection, current and nadir CD4 T-cell count and length of virologic suppression. We evaluated baseline levels and cytokine-induced fold change increases of pSTAT1, pSTAT3, and pSTAT5 in B cells, CD4 and CD8 T-cells, and monocytes using flow cytometry. Comparisons between pSTAT levels in HIV-infected and uninfected subjects and in younger and older HIV-infected subjects were made using the Wilcoxon rank sum test. We corrected for multiple comparisons with the Benjamini-Hochberg procedure with significance assessed at the α=0.05 level.

Results: Median current and nadir CD4+ T-cell counts in the HIV-infected subjects were 559 and 220 cells/uL, respectively. Clinical characteristics were similar between older and younger HIV-infected subjects, other than a lower current median CD4+ T-cell count in the older subjects (523 vs. 772 cells/uL; p=0.02). HIV-infected subjects demonstrated significantly altered STAT signaling compared to uninfected individuals. The STAT3 pathway, which negatively regulates the Type-I interferon-mediated antiviral response and is associated with proliferative responses, showed the most dramatic differences between HIV-infected and uninfected subjects, ($p<0.001$ for many of the comparisons). STAT3 signaling in monocytes and CD4 and CD8 T cells in HIV-infected individuals displayed a phenotype consistent with early aging and poor immune functioning. However, this pattern was not consistent across all STATs and all cell types. For instance, in monocytes, cytokine-inducible STAT1 protein levels were increased in HIV-infected individuals compared to uninfected individuals. Interestingly, in HIV, there did not appear to be an additive effect of aging on pSTAT levels. Higher baseline levels of pSTAT3 were associated with a history of low nadir CD4 T-cell count.

Conclusions: HIV is associated with widespread signaling defects. Abnormalities in cytokine-induced pSTAT3 suggest potential persistent proliferative defects in treated HIV. However, cell signaling abnormalities in HIV are a unique phenotype that do not mirror all features found in aging uninfected individuals. Aging did not lead to worsened cell-signaling in HIV, suggesting that HIV's effect on the immune system may obscure any additional adverse effects from aging. The association of elevated baseline pSTAT3 in HIV subjects with low nadir CD4 (a risk factor for the development of age-associated co-morbidities) indicates that, in humans, STAT3 might also play a role in suppressing the anti-viral response.

Abstract: O_02

Leukocyte telomere length in HIV-infected and HIV-Exposed Uninfected Children; shorter telomere length with uncontrolled HIV viremia

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Background: Nucleoside reverse transcriptase inhibitors (NRTIs) inhibit human telomerase reverse transcriptase. Telomerase activity expressed in stem cells limits telomere shortening that takes place during cellular division. Exposing developing fetuses or children to NRTIs could potentially accelerate telomere attrition and affect the aging process.

Material & Methods: In this prospective study, blood was collected from HIV+ and HIV-exposed uninfected (HEU) children and youth (0-19 years) enrolled in the CARMA cohort study on HIV therapy and aging. For HIV- controls, only age and gender were known. Leukocyte telomere length (LTL) was measured using a qPCR-based assay. Univariate linear regression models were used to examine relationships of explanatory variables with LTL. Univariately important variables were used as candidates in the development of three distinct multivariate models for:
a) all subjects (HIV+/HEU/HIV-),
b) HIV+/HEU subjects only,
c) HIV+ subjects only.

Results: LTL data was obtained for94 HIV+ (median age in years 13.3, IQR [9.9-15.8]), 177 HEU (2.0 [0.6-4.0]), and 104 HIV- control (10.6 [5.3-14.2]) children. All HEU children were exposed to ART perinatally, in utero and/or post-natal prophylaxis. After adjusting for age and gender, there was no difference in LTL between the 3 groups. In all final multivariate models, older age ($p<0.001$) was associated with shorter LTL. For the three groups together ($p=0.04$) and the HIV+ group ($p<0.001$), male gender was also associated with shorter LTL. For the HIV+ group alone, apart from older age and male gender, having a detectable HIV viral load was strongly associated with shorter LTL ($p=0.01$).

Conclusions: In agreement with other studies, older age and male gender were associated with shorter telomeres. Interestingly, a gender relationship with LTL was observed despite the fact that 60% of subjects were under 9 years of age. While our conclusions about the role of HIV status are limited by the age imbalance between the groups, our study did not detect any meaningful association between HIV status or perinatal ART exposure and children's LTL, a reassuring finding. However our results also suggest that in HIV+ children, uncontrolled HIV viremia rather than ART exposure is associated with acceleration of blood telomere attrition.

Abstract: O_03

Age Modifies the Associations Between Tumor Necrosis Factor Mediated Inflammation with Clinical and Immune Outcomes in HIV-Infected Individuals

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Objective: To examine contributions by age to associations between TNF-mediated inflammation and survival, or naive CD4 cell restoration within two different study populations.

Methods: Associations with survival used Cox proportional hazards models, in a randomized controlled trial of prednisolone combined with tuberculosis therapy in HIV-infected Ugandans with TB. Associations with naive CD4 cell restoration used mixed-effects models among participants who initiated antiretroviral therapy (ART) in a prospective, multicenter cohort (ACTG 5015).

Results: 190 HIV infected patients with TB who began antituberculosis therapy were randomized to receive prednisolone or placebo. Associations between survival and baseline TNF-a and sTNFR2 levels depended on age, where higher mortality was associated with higher baseline plasma TNF-a and sTNFR2 levels among younger (≤30 years), but not older (>30 years) patients [Table 1].

Table 1

Baseline Independent Variables	**Age ≤ 30 years** HR (95% CI)	**Age >30 years** HR (95% CI)	**P-value for Interaction with Age***
sTNFR2 *P*	1.37 (1.13-1.65) 0.002	0.88 (0.51-1.53) 0.16	0.04
TNF-a *P*	4.67 (1.59-13.76) <.0001	1.08 (0.98-1.19) 0.82	0.19
Deaths	11	20	

*adjusted for baseline CD4, LVL & Karnofsky score, and sex

Among 90 ART naive subjects who began ART in a prospective age-differentiated cohort (ages ≤30 or ≥45 years), increases in naive CD4 cells with ART were associated with lower time-varying plasma TNF-a and sTNFR2 levels, and with lower proportions of CD8 cells that expressed CD95 (Fas) and HLA-DR/CD38 among younger, but not older subjects [Table 2].

Table 2

Time-Varying Independent Variables	**Age ≤ 30 years** DCD4 naive cells/mL (95% CI)	**Age ≥45 years** DCD4 naive cells/mL (95% CI)	**P-value for Interaction with Age***
sTNFR2 *P*	-12.14 (-21.65, -2.62) 0.02	0.19 (-1.13, 1.50) 0.30	0.01
TNF-a *P*	-2.72 (-4.71, -0.72) 0.01	0.29 (-0.60, 1.19) 0.49	0.005
%CD8+/CD95+ *P*	-2.05 (-2.81, -1.30) <.0001	-0.57 (-1.43, 0.30) 0.19	0.02
%CD8+/HLA-DR+/CD38+ *P*	-1.98 (-2.58,-1.38) <.0001	-0.69 (-1.33, -0.057) 0.03	0.01

*adjusted for time-varying CD4 and LVL, and sex.

Conclusions: Associations between death or naive CD4 cell restoration with TNF-mediated inflammation were significantly different between older and younger HIV-infected individuals. This interaction with age may imply different mechanisms of immune restoration or destruction according to age.

Abstract: O_04

High Levels of Fibroblast Growth Factor–1 May Protect Against Neurocognitive Impairment among HIV-infected Individuals with the ApoE-e4 Allele

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Background: Mild and moderate forms of HIV-associated Neurocognitive Disorders (HAND) remain prevalent despite improved longevity and survival of HIV-infected persons with antiretroviral treatments (ART). The exact underpinnings of HAND remain to be elucidated, and genetic factors that have been found to predispose persons to Alzheimer's Disease (i.e., apolipoprotein E-ε4 allele; ApoE-ε4) may also be associated with HAND, particularly among older adults. In contrast, neurons may be protected from the neurotoxic effects of HIV by higher levels of fibroblast growth factors (e.g., FGF-1), which promote neuronal survival. Given this background, we hypothesized that higher levels of FGF-1 may serve as a neuroprotectant among HIV-infected persons who also possess the ApoE-ε4 allele.

Materials & Methods: Sixteen HIV-infected participants (mean age = 42.4) completed a comprehensive laboratory, neuromedical and neuropsychological evaluation. Standardized clinical ratings were utilized to determine neurocognitive impairment (NCI) based on the presence of impaired performance in at least two of seven domains evaluated. FGF-1 was measured by commercial enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN). ApoE-ε4 carrier status was directly genotyped in isolation. Participants were divided into four groups based on ApoE-ε4 status (+/-) and plasma FGF-1 levels (High/Low divided at group mean). Chi-Square analysis was used to assess the association between these four groups and NCI. Logistic regression was used to assess the influence of other common HIV disease variables and cofactors that may contribute to NCI.

Results: The association between ApoE-ε4 (+/-) and FGF-1 levels (high/low) on NCI was significant (Chi-Square LR = 16.5; $p < 0.001$). Participants who were ApoE-ε4-negative were unlikely to be classified as NCI regardless of plasma FGF-1 status (14%, 1/7). Among ApoE-ε4-positive participants, all participants with low plasma FGF-1 levels were classified as NCI (100%, 6/6), whereas ApoE-ε4-positive participants with high plasma FGF-1 levels were not classified with NCI (100%, 3/3). When other factors often thought to be associated with NCI were modeled in the context of FGF-1 levels and ApoE status (e.g., CD4 count, nadir CD4 count, on/off ART treatment, Hepatitis C Status), FGF-1 and ApoE remained significantly associated with NCI ($p's < .05$).

Conclusions: These preliminary findings suggest that FGF-1 may be neuroprotective against the risks of HAND that are conferred by the presence of the ApoE-ε4 allele. In other words, FGF-1 may counteract the relative inefficient and deleterious response to CNS stressors (i.e., HIV infection) that has been associated with instability of the ApoE-ε4 isoform (Mahley & Huang, 2006). Such biomarker-gene interactions may be especially relevant for older HIV-infected adults, who are particularly vulnerable to HAND and for whom the ApoE-ε4 allele is an independent risk factor for neurotoxicity. Although the sample size in this study is small, these findings may indicate that FGF-1 is an important factor to consider in examining APOE-ε4-related risk for HAND, and suggest the possibility that exogenously-administered FGF-1 might help to ameliorate neurocognitive problems associated with HIV infected persons who are APOE-ε4 carriers.

Abstract: O_05

Prevalence of and Risk Factors for Frequent Falls in HIV-1 Infected Persons

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Background: Falls are experienced each year by approximately 30% of persons aged ≥ 65 years, are costly, and are associated with significant morbidity. Persons with HIV-1 infection are at risk for accelerated aging and may also be at increased risk for early fall-related morbidity. The incidence of and risk factors for falls in HIV-1-infected persons are unknown.

Material & Methods: Cross-sectional study of 45 to 65 year-old HIV-1-infected subjects, on anti-retroviral therapy (ART) >6 months, with plasma HIV-1 RNA <48 copies/mL. Subjects were verbally questioned about falls in the year prior. Physical function assessments, medical diagnoses and current medications were collected. Characteristics of frequent fallers (≥2 falls in past 12 months) and non-fallers (no falls) were described by mean and standard error for continuous, and frequency and percentage for categorical measures. Risk of frequent falling was described with odds ratios (OR) and 95% confidence intervals (CI), and tested with Wald chi-square.

Results: 359 subjects entered the study. 250 persons (70%) reported no falls; 109 (30%) had at least 1 fall; 66 (18%) were frequent fallers. Age was similar between frequent fallers (52.4 ± 0.3 years) and non-fallers (52.0 ± 0.6 years; p=0.6). Current CD4 count (599 vs 595 cells/mL), nadir CD4 count (163 vs 168 cells/mL), and duration of continuous ART (101.0 vs 98.0 months) were similar (p>0.8) between frequent and non-fallers, respectively. Frequent fallers had a slightly longer time since HIV-1 diagnosis (15.8 vs 14.0 years, p=0.09) and greater odds of lipoatrophy (OR 2.0; CI 1.1, 3.7; p=0.02). Odds of frequent falls were higher in females (OR 2.5; CI 1.3, 4.8), smokers (OR 2.1; CI 1.2, 3.4), and persons with diabetes (OR 5.6; CI 2.6, 12.1), psychiatric disease (OR 3.7; CI 1.9, 6.9), cardiovascular disease (OR 3.0; CI 1.4, 6.8), arthritis (OR 3.2; CI 1.5, 5.5), chronic pain (OR 4.6; CI 2.6, 8.2), neuropathy (OR 3.2; CI 1.8, 5.6), or dementia (OR 8.2; CI 2.0, 33.9) (all p<0.01). Use of beta-blockers (OR 3.6; CI 1.8, 7.3), diabetes medications (OR 4.5; CI 2.0, 10.2), antidepressants (OR 4.6; CI 2.6, 8.1), anti-psychotics (OR 3.9; CI 1.9, 8.1), benzodiazepines (OR 2.8; CI 1.4, 5.3), or narcotic pain medications (OR 5.5; CI 3.1, 9.8) was significantly higher among frequent fallers than non-fallers (all p <0.01). Frequent fallers had weaker grip strength (OR 4.7; CI 2.2, 10.0; p<0.001), greater difficulty rising from a chair (OR 2.6; CI 1.3, 5.3; p=0.006), greater difficulty with balance (OR 13.7; CI 4.2, 44.0; p<0.001), and slower gait speed on 400 m walk (1.5m/s vs 1.3m/s; p<0.001). The odds of frequent falls was over 9-fold greater among those with frailty by Fried's definition (OR 9.3; CI 3.6, 24.3; p <0.001) than non-frail persons.

Conclusions: The risk of falling for middle-aged HIV-1 infected persons is consistent with that reported in non-HIV-infected populations aged ≥ 65 years. High fall risk is associated with common comorbidities and corresponding medications. Fall risk should be assessed routinely in middle-aged HIV-1-infected persons and the effectiveness of interventions to prevent falls in HIV-infected persons should be explored.

Abstract: O_06

Frailty and Incident Hospitalization in a Cohort of HIV-Infected and Uninfected Injection Drug Users (IDUs)

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Background: Frailty, a syndrome of diminished physiologic reserve with increased stressor vulnerability, predicts hospitalization, disability and mortality in older HIV-uninfected adults. A prefrail state has also been defined as a precursor to frailty and subsequent disability. We evaluated the effect of HIV, immune status, and viral suppression on frailty and prefrailty, and the impact of frailty on subsequent hospitalization in an aging IDU cohort.

Methods: Frailty, defined by the presence of ≥3 of 5 standard criteria: weakness (grip strength), slowed walking speed, weight loss, low physical activity and exhaustion, was assessed biannually among a cohort of current and former injectors from 2005-2009. Correlates of frailty and prefrailty (defined by the presence of 1-2 of the 5 frailty criteria), were assessed using repeated measures multinomial logistic regression. Cox proportional hazards models estimated risk for incident hospitalization.

Results: Of 1206 subjects at baseline, the median age was 48 years and 345 (28%) were HIV+. The prevalence of frailty was 8.3% and of prefrailty was 59%. In multivariable analysis of 4,652 person-visits, both frailty and prefrailty were positively associated with age, female gender, socioeconomic status, depressive symptoms, and HIV status. Adjusting for these factors, HIV+ individuals with a CD4 <350 and detectable HIV RNA had a 1.5-fold higher likelihood of being prefrail (OR, 1.49; 95%CI 1.17-1.89) and a 2.3-fold higher likelihood of being frail (OR, 2.26; 95%CI 1.51-3.39) compared to HIV-negative individuals, while no increased risk was seen for those with higher CD4 counts or with HIV virologic suppression. In a separate multivariable model and compared to HIV-negative persons, the odds of frailty for HIV+ individuals on HAART was 1.5-fold higher (OR, 1.53; 95% CI 1.03, 2.26) but was >2-fold higher for HIV+'s not on HAART (OR, 2.04; 95%CI 1.38-3.03). Controlling for hospitalization risk associated with sociodemographics, alcohol use, hepatitis C, and advanced HIV disease, frailty was an independent predictor of incident hospitalization (adj HR 1.5; 95%CI 1.04-2.17).

Conclusion: Our data suggest that HIV infection, particularly with inadequate virologic control, is significantly associated with frailty among IDUs. Among aging, at risk IDUs, frailty assessment can inform prediction of clinical endpoints like hospitalization. Further exploration of the underlying biological mechanisms and clinical utility of frailty may inform management of aging HIV-infected persons.

Abstract: O_07

Additive effects of aging and HIV infection on semantic verbal fluency: A view of the cortical hypothesis through the lens of clustering and switching

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Introduction/Background: Recent findings of the neuropathological changes observed in older HIV-infected adults (e.g., cortical beta-amyloid) suggest that the increased neural burden of HIV and aging may lead to a neuropsychological profile akin to that observed in cortical dementias (e.g., degradation of semantic memory). This study sought to evaluate this hypothesis by examining semantic fluency and its component processes (i.e., clustering and switching) in older HIV-infected adults. As clustering is commonly associated with the integrity of the semantic memory system and may be dissociable from switching, which is more closely associated with executive functions and underlying frontostriatal loops, an examination of these component processes may provide a useful framework to explore the cortical hypothesis in older HIV-infected adults.

Material & Methods: Participants included 257 individuals across 4 demographically matched groups: Younger (i.e., ≤40 years) Healthy (n=93), Younger HIV-infected (n=50), Older (i.e., >50 years) Healthy (n=51), and Older HIV-infected (n=63) individuals. Participants were administered a standard semantic fluency protocol scored according to established clustering and switching guidelines (Troyer et al., 1997) as part of a comprehensive neuropsychological evaluation in our HIV Neurobehavioral Research Program (HNRP).

Results: Jonckheere-Terpstra tests revealed significant additive effects for overall semantic fluency output (p = 0.001) and switching (p = 0.015), with the lowest performance in the Older HIV-infected group. Specifically, the Older HIV-infected cohort demonstrated poorer switching performance relative to the Younger HIV-infected (p = 0.025; d = -0.51) and seronegative groups (p < 0.001, d = -0.70), although performed comparably to the Older HIV-seronegative adults (p = 0.473, d = -0.13). Nevertheless, older HIV-infected individuals with HIV-associated neurocognitive disorders (HAND; n = 27) demonstrated significantly worse switching relative to the unimpaired older HIV-infected participants (p = 0.004, d = -0.68) and older HIV-seronegative group (p = 0.016, d = -0.48). No significant between-group effects were found for cluster size (ps > 0.05). Results were not better explained by confounding psychiatric, medical, or HIV-disease characteristics. Within the older HIV-infected adults, poorer switching was associated with learning and executive dysfunction (ps < 0.05), but not with semantic memory impairment (p = 0.226), and was a significant predictor of functional decline (p < 0.05), even when considering potentially confounding variables (e.g., affective distress).

Conclusions: Results suggest that HIV infection and aging may confer adverse additive effects on the executive components of semantic fluency (i.e., switching), which may reflect the combined frontostriatal neuropathological burden of these two conditions. These findings are consistent with the executive (i.e., switching) deficits found in other conditions characterized by frontostriatal damage (e.g., Parkinson's disease; Troyer et al., 1998), and argue against a posterior neocortical pattern of neuropsychological impairment associated with HIV and aging. Nonetheless, these findings provide support for an increased risk for cognitive impairment and subsequent functional decline in older HIV-infected individuals, and highlight the need to address increased neurocognitive morbidity in this growing subpopulation of the HIV epidemic.

Abstract: O_08

Prospective Comparison of Three Functional Assessments with the Veteran's Aging Cohort Study Index in Virologically Suppressed HIV-Infected Adults

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Background. Assessment of functional status is necessary to understand the impact of human immunodeficiency virus-1 (HIV-1) on successful aging and preservation of independence, but little is known about the performance of functional status instruments in non-elderly or HIV-1 infected persons. We compared three instruments for assessment of physical function status with each other and with the Veteran's Aging Cohort Study (VACS) mortality risk index in a middle-aged HIV-1-infected cohort.

Methods. 45 to 65 year old HIV-infected subjects with plasma HIV-1 RNA <48 copies/mL on >6 months of antiretroviral therapy were identified as high, moderate, or low function by Fried's Frailty Phenotype (FFP), the Short Physical Performance Battery (SPPB), and the 400m walk. VACS scores were calculated. A weighted kappa statistic was used to assess agreement. Logistic regression and unequal variance t-tests were used for tests of dichotomous and continuous outcomes, respectively; 95% confidence intervals were reported for corresponding odds ratios (OR) and standard errors with mean differences.

Results. 359 subjects were enrolled. Mean age was 52 (SE 0.3) years, 85% were male, 18% Hispanic, 74% Caucasian, mean CD4 count 594 (SE 16) cells/mL, and 95% had plasma HIV-1 RNA <48 copies/mL. The three assessment instruments had fair agreement (61-64%, weighted Kappa 0.34-0.41) and 31-51% of subjects had moderate and 3-7% had high impairment. Three percent of subjects were unable to complete the 400m walk test; 50% were unable to maintain a walking speed above 3.4 miles/hour, meeting a criterion for Social Security Administration disability; 7% met frailty criteria by FFP and disability by SPPB. Low functional status was associated with higher odds of hospitalization (OR 4.3-10.9), higher numbers of comorbidities (OR 1.8-2.5)and medications (OR 2.5-3.3), greater reports of pain (OR 6.2-26.8), and lower reported physical activity (OR 5.5-11.2) across all instruments (p=0.01). Low function defined by FFP was associated with higher odds (p<0.01) of tobacco use (OR 3.6; CI 1.6-8.24), psychiatric disease (OR 4.2; CI 1.61-10.9), neurological disease (OR 6.1; CI 1.7-21.5), and frequent falls (OR 21.7; CI 7.4-63.3). SPPB-defined low function was associated with higher odds (p<0.01) of diabetes (OR 7.6; CI 2.8-21.0), arthritis (OR 3.3; CI 1.5-7.6), neurological disease (OR 8.6; CI 2.4-30.6), and frequent falls (OR 12.8; 4.6-35.6). Failure to complete the 400m walk was associated with higher odds (p<0.01) of obesity (OR 7.1; CI 2.0-25.1), diabetes (OR 9.1; CI 2.2-37.1), arthritis (OR 6.6; CI 1.7-25.3), and lung disease (OR 20.1; CI 5.4-74.8). Low- versus high-functioning groups had differences in VACS scores: SPPB, 12.4 (SE 2.8; p=0.001); FFP, 8.6 (SE 2.8; p=0.03); and 400m walk, 11.9 (SE 4.2; p=0.08).

Conclusions. The three instruments for assessment of physical function identified low functioning persons with distinct clinical characteristics and higher mortality risk as predicted by the VACS mortality risk index. Measurement of functional status, identification of risk factors that may lead to functional compromise, and interventions to reduce risks could improve successful aging and maintenance of independence as persons with HIV age.

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Abstract: O_09

Improvement of Quality of Life after the Application of Mindfulness-Based Cognitive Therapy in Subjects Aging with HIV Infection

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Background: Mindfulness-Based Cognitive Therapy (MBCT) is designed to help people who suffer episodes of depression and chronic unhappiness. It combines the ideas of cognitive therapy with meditative practices and attitudes based on the cultivation of mindfulness. The efficacy of MBCT in HIV population to improve quality of life has not been proved yet.

Material & Methods: Forty HIV-1 infected subjects (20 men and 20 women) were randomized to either participate in a MBCT program consisting of eight weekly two-hour classes with weekly assignments to be done outside of session (intervention group) or continue with their routine care visits (control group). Data collected included demographic and clinical variables. Quality of life was assessed with Nottingham Health Profile (NHP) questionnaire, which has 38 statements that assess 6 different dimensions of normal living: energy, pain, emotional reactions, sleep, social isolation and physical mobility. Scores for each dimension can range from 0 "no problems" to 100 "all problems listed are present". Statistical summaries were prepared for the main variables. Continuous variables were described as median (IQR) and categorical variables as percentages (number of patients). Univariate linear regression analyses were fitted to evaluate the difference between pre and post measurements considering the group of treatment as explanatory variable.

Results: The demographic and clinical characteristics of the sample were: mean (SD) age: 50 (46-52), years since HIV-1 infection: 20 (16-24), years on ART: 16 (12-18), nadir CD4: 156 (68-253) cell/mm^3, current CD4: 527 (364-633) cell/mm^3, CV<25 copies in 39 subjects. After the application of the MBCT program, the intervention group reported an improvement in all the dimensions of normal living evaluated when compared with the control group: energy (Coef. -31.20; p=0.012), pain (Coef. -19.26; p=0.038), emotional reactions (Coef. -29.09; p=0.001), sleep (Coef. -18.04; p=0.027), social isolation (Coef. -30.22; p=0.001) and physical mobility (Coef. -11.77; p=0.008).

Conclusions: Quality of life improved very importantly after the implementation of MBCT in this sample of long-term diagnosed HIV infected subjects. MBCT may be a recommendable strategy to improve the quality of life of subjects aging with HIV infection.

Abstract: O_10

Visualization at encoding improves prospective memory in older adults living with HIV infection

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Background: Prospective memory (PM), or "remembering to remember", is commonly impaired in older adults living with HIV infection and is strongly associated with poorer everyday functioning outcomes (e.g., medication non-adherence). The current study aimed to improve PM among a sample of older HIV-infected adults by using a visualization intervention, which prior research suggests may enhance memory performance by deepening encoding.

Materials & Method: Participants included 70 HIV-infected adults aged 50 and older (M = 56 ± 6 years) who had an estimated duration of HIV infection of 18 ± 7 years. The study sample was 83% male, 70% Caucasian, and had obtained 14 ± 3 years of education. At the time of their neuropsychological evaluation, 91% of the sample was prescribed combination ART, 7% had CD4 counts below 200 cells/μL, and 15% had detectable HIV RNA in plasma. All study participants were given a PM intention in which they were asked to perform a medication management task at a prespecified future cue (i.e., when the examiner showed them the grooved pegboard approximately 1 hr into their neurocognitive evaluation). Subjects were randomized into either: 1) a visualization (VIS; n = 32) arm in which they were asked to repeat the instructions and spend several moments visualizing the physical similarities between the cue (i.e., the pegboard) and the intention (i.e., the medication management pillbox) stimuli, or 2) a control (CTL; n = 38) arm in which they simply repeated the instructions.

Results: Participants in the visualization condition were significantly more likely than controls to successfully complete the medication management PM task when shown the grooved pegboard (VIS = 55% vs. CTL = 30%, $p < .05$). The effect of visualization was particularly strong for participants with lower baseline PM functioning as measured by a separate, standardized clinical test (VIS = 46% complete vs. CTL = 17% complete, $p \leq .05$) versus subjects with normal PM (VIS = 61% complete vs. CTL = 47% complete, $p > .20$).

Conclusions: This study demonstrates that a brief strategic visualization exercise can enhance PM functioning in older HIV-infected adults. These findings may inform the development of targeted cognitive neurorehabilitation interventions to improve everyday functioning outcomes (e.g., adherence) and health-related quality of life in this population.

Abstract: O_12

Pharmacokinetics of Two Common Antiretroviral Regimens in Older HIV-Infected Patients: A Pilot Study

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Background: With improved antiretroviral (ARV) treatment, patients with chronic HIV infection are living longer. Known physiologic changes with aging may alter ARV pharmacokinetics (PK), but these alterations have not been defined in this population. In preparation for a large, longitudinal sparse sampling study in older HIV-infected patients, this study was conducted to develop population PK models for 4 ARVs in aging patients.

Materials and Methods: This was an open-label pilot PK study of 12 non-frail (by phenotype) HIV+ adults >55 years of age, receiving tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV; n = 6) or TDF/FTC/ atazanavir/ritonavir (ATV/r; n = 6) for clinical care for >2 weeks. Eleven plasma samples over one 24 hour visit were analyzed using validated HPLC/UV methods. Noncompartmental PK using Phoenix Win Nonlin and PK modeling using Monte Carlo Expectation Maximization (MC-PEM in S-Adapt with S-ADAPT TRAN) were performed for each drug. Area under the curve (AUC) and maximum concentration (C_{max}) were compared to published values from HIV+ patients using the Wilcoxon rank-sum test. Data are reported as mean ± SD.

Results: Subject age was 59.7 ± 3.9 years, BMI was 29.9 ± 5.4 kg/m^2, CrCL was 70.1 ± 17.6 ml/min and CD4+ lymphocytes were 818 ± 370 cells/mm^3. 3 Caucasians and 3 African Americans were enrolled on each regimen, and 6/12 of all subjects were female. Subjects received their regimen for 41 ± 33 months: 11/12 had undetectable HIV RNA with 100% self-reported adherence. Compared to published values, the AUC and C_{max} of tenofovir (TFV) were 7-13% lower in these subjects, while the AUC and C_{max} of FTC were 25-75% higher. For EFV and ATV, AUC was similar but C_{max} was 12-15% lower. These differences did not achieve statistical significance (as expected given the small sample size). TFV, FTC, EFV, and ATV were each well-described by a two-compartment linear model with first-order absorption. Estimated weight-adjusted oral clearances (CL/F) for each drug were similar to historical controls, but variable: TFV/FTC/ATV = 5.6 ±2.3; 3.7 ±1.5; 1.9± 1.1 mL/min/kg, respectively; TFV/FTC/EFV = 7.1 ± 6.1; 3.2 ± 0.7; 2.1 ± 0.8 mL/min/kg, respectively.

Conclusions: For TFV, EFV, and ATV, small decreases in AUC and C_{max} were observed; FTC demonstrated increases in AUC and C_{max}. For TFV and FTC, CL/F exceeded estimated CrCL in all subjects, implying that renal filtration and secretion are intact. Although TFV and FTC are primarily renally cleared, decreased renal function does not explain these findings of decreased TFV and increased FTC exposures. Higher EFV and markedly lower ATV exposures were expected, but were not observed. Intracellular metabolite (TFV diphosphate and FTC triphosphate) and protein-free (ATV and EFV) concentrations remain to be analyzed, and may provide additional insight into altered ARV efficacy or toxicity in the aging population. As only non-frail subjects were enrolled, future population PK studies will include frail individuals to determine if frailty contributes to altered ARV PK and efficacy, and younger subjects for direct comparisons of parameters and variability. PK investigations in aging patients are critical to optimally treat this growing population.

Abstract: O_13

Co-effect of HIV-1 infection and ageing on renal function

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Background: Mortality since HAART has resulted in longer survival and getting older resulting in an increased incidence and prevalence. Such a shift is seen locally at the Chelsea and Westminster Hospital which has the largest HIV treatment centre in Europe with a cohort of over 15,000 since 1988. As age increases there is a need for assessing and monitoring clinical factors that have are associated with ageing. This study analyses the relationship between renal function, increasing age and ARV class exposure. Renal function has been reported to deteriorate with exposure to NRTI and boosted and non-boosted PI.

Materials & Methods: The association between ageing, renal function as expressed by estimated glomerular filtration rate (eGFR) and exposure to NRTI, PI and NNRTI drugs was assessed. Patients exposed to these drugs were grouped by age: 'younger', 18-39; 'middle', 40-49; and 'older' adults, greater than 50 years. A random intercept model using MIXED procedure in SAS was generated by fitting all eGFR results as a dependent variable by changing age group strata, stratified by their exposure to ARV drug classes. In the UK the normal age standardised eGFR is greater than 90 whilst eGFR between 60 and 90 ml/min is considered stage 2 chronic kidney disease and is considered mildly reduced kidney function.

Results: Of 15,048, 87% were men, 65% Caucasians 82% MSM. For ART naïve, young adults had a mean eGFR 83.5 compared with 77.5 ml/min for the older adults (p<0.001). The latter's mean eGFR was also significantly lower compared with the mean of the middle adults: 77.5 versus 80.5 ml/min respectively (p=0.001). For those who had exposure to only NRTs and PI classes, the younger adults had a mean of 82.2 compared with 74.7 ml/min for older adults (p<0.001). The mean eGFR in older adults was lower compared with middle adults: 74.7 versus 79.0 ml/min (p=0.001). Those exposed to only NRTs and NNRTI class of ARV drugs, the younger adults had a mean of 83.5 compared with 77.7 ml/min for older adults (p<0.001). The mean eGFR of older adults was also significantly lower compared with the mean of the middle adults: 77.7 versus 80.9 ml/min respectively (p=0.001). For those who had been exposed to NRTs, PI and NNRTI classes, the mean eGFR was 82.8 in younger compared with 74.7 ml/min for older adults (p<0.001). The mean eGFR of older adults was also lower compared with the middle adults: 74.7 versus 78.9 ml/min respectively (p=0.001).

Conclusion: The reduction seen in ART naïve and experienced patients demonstrated a deterioration of renal function in addition to age-related changes as eGFRs are age-standardised markers of renal function. In addition to a decline in renal function due to ageing and HIV disease, ARV drugs may add to this. Specific drugs may be associated with renal impairment this was not observed at ARV drug classes. Further analyses of specific drugs may show long-term renal impairment but PLHIV on and off ART need to have their renal function checked at regular intervals as part of their routine management.

Abstract: O_14

Some HIV protease inhibitors induce premature senescence and alter osteoblastic cell fate determination of human bone marrow mesenchymal stem cells

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Background: HIV-infected patients, treated with combination Antiretroviral Therapy (cART) prematurely present an increased prevalence of age-related co-morbidities, such as osteoporosis. The proposed pathogenic candidates mediating cART-induced osteopenia include viral infection and the drug regimen itself. Protease inhibitors (PIs) have been suspected to induce bone loss but the precise mechanisms involved are unknown. Bone mass and turnover are maintained by the coordinated balance between bone formation by osteoblasts and bone resorption by osteoclasts. It has been previously shown in endothelial cells, that some PIs can induce the accumulation of farnesylated prelamin A, a biomarker of cell aging leading to cell senescence. We hypothesized that some PIs could induce premature aging of osteoblast precursors, namely bone marrow mesenchymal stem cells (MSCs), and reduce their capacity to differentiate into osteoblasts.

Material & Methods: Senescence was studied in proliferating human adult bone marrow MSCs after a 30-day exposure to atazanavir (ATV) or lopinavir (LPV) at near Cmax concentrations, with or without boosting concentrations of ritonavir (RTV, ATV/r and LPV/r). The cell fate of MSCs was assessed by studying their capacity to differentiate into osteoblasts and adipocytes. Then, MSCs were cotreated or not with pravastatin for 15 days to evaluate a potential reversion/prevention effect.

Results: When compared to non-treated cells, long-term ATV- and LPV-treated MSCs had a reduced proliferative activity that worsened with increasing cellular passages. LPV/r and to a lesser extent ATV/r chronic exposure led to increased oxidative stress. Senescence-associated beta-galactosidase activity and expression of cell cycle inhibitors (p21WAF1 and p16INK4A) were also increased, indicating the occurrence of premature cell senescence. Because age-related bone loss is associated with increased bone marrow fat, we evaluated the impact of PI-induced senescence on the capacity of MSC to differentiate towards the osteoblastic and adipogenic lineages, after 30-day PI-exposure. We observed that PI-induced premature senescence altered the adipocyte/osteoblast differentiation balance. Whereas osteoblast and adipocyte differentiation were significantly decreased by LPV/r treatment, ATV/r-treated MSC showed decreased osteoblast differentiation but enhanced adipogenesis. After 30 days of chronic treatment with PIs, we observed prelamin A accumulation. Blocking its farnesylation, using statins, has been shown to ameliorate cellular senescence phenotypes of accelerated ageing. Thus we investigated the impact of pravastatin, to prevent or reverse the PI-effect of on MSCs. We found that it was able to prevent PI-induced senescence, to reduce oxidative stress and to restore the differentiation potential of PI-treated MSC, towards the osteoblastic lineage.

Conclusion: These in vitro data show that some PIs alter osteoblast formation by directly inducing premature senescence and affecting the osteoblast differentiation potential of MSCs. Thus, they corroborate the clinical data. Moreover, we found that pravastatin treatment can prevent PI-induced premature senescence. Overall, these results allow new insight into the pathophysiological mechanisms of PI-induced decreased bone mineral density in HIV-infected patients.

Abstract: O_15

Menopause Associated with Higher Numbers of Comorbidities among Women Aging with HIV

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Introduction: The aging of the population living with HIV has garnered increasing attention as the CDC estimates that half of this group will be 50 years or older by mid decade. Women account for at least 25% of the HIV population age 50 and older. They may encounter unique issues as they age with this disease. The intersection of HIV and aging is manifested by the early onset of many comorbid conditions typically associated with more advanced age. Furthermore, the average number of comorbid conditions in this population is significantly greater than among community dwelling adults 70 years and older (i.e., 3.3 vs. 1.1 , respectively). Age is characterized by a broad constellation of biological and social changes all of which interact with HIV. Some of those interactions may contribute to the observed increases in comorbid conditions. Among women, menopause represents a biological milestone of the aging process. Some research suggests that women may be at an increased risk for illnesses following menopause, particularly cardiac diseases. Yet we know little about how menopause is related to the experience of comorbid health conditions among women aging with HIV.

Method/Results: We examined these relationships among the 264 women who participated in the *Research on Older Adults with HIV* (ROAH) study. The average age of these women was 55.2 years, and the majority was non-Hispanic Black (58%) or Hispanic (34%). The average length of time since HIV diagnosis was 11.4 years, and 45% had an AIDS diagnosis. We examined the relationships between self-reports of menopause and 22 comorbid conditions and the total number of comorbid conditions reported. We controlled for age in all analyses. Among this sample, 44% reported menopause. There were no significant differences between the pre-menopause and menopause groups with regard to length of HIV infection or AIDS diagnosis. Those who reported menopause had significantly higher CD-4 counts than the pre-menopausal group (i.e., CD-4 500 or greater 60% and 41%, respectively). Those who were menopausal were significantly more likely to report arthritis, dermatological problems, hearing loss, hepatitis, hypertension, menstrual difficulties, nervous system disorders, neuropathy, respiratory conditions, and other sexually transmitted infections. Among premenopausal women, the average number of comorbidities was 2.8 as compared to 4.7 on average in the menopause group [$F(1,259) = 15.8$, $p < .001$].

Conclusions: These findings suggest that post-menopausal women with HIV are at a significantly greater risk for developing comorbid health conditions as they age. Health care providers should pay careful attention to the onset of menopause and its impact on the health of their older HIV-positive female patients. More research is needed to better understand the interaction between HIV infection, aging and the onset of menopause, in order to develop effective treatment and care paradigms to meet the needs of this growing population.

Abstract: O_16

Cytomegalovirus IgG antibody is associated with subclinical carotid artery disease among HIV-infected women

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Background: Cytomegalovirus (CMV) is a β human herpesvirus that remains latent or persistent within the host. Chronic lifetime exposure to CMV may contribute to accelerated immunologic aging, atherosclerosis, cognitive decline, and other age-dependent chronic diseases. In the general population, CMV infection has been linked to carotid atherosclerosis, development of cardiovascular diseases and increased mortality. CMV co-infection in HIV-infected individuals has been implicated in immune activation and accelerated progression of immunodeficiency. Because HIV-infected individuals have increased cardiovascular risk, we hypothesized that CMV is associated with subclinical vascular disease in HIV-infected adults.

Material & Methods: Among 644 HIV-infected and 100 HIV-uninfected participants in the Women's Interagency HIV Study (WIHS), we performed B-mode carotid artery ultrasound and brachial artery blood pressure measurements. CMV IgG antibody titers were measured concurrently with cardiovascular assessments. We examined the association of CMV IgG with carotid artery intima-media thickness, carotid artery distensibility, Young's elastic modulus, systolic and diastolic blood pressures, and pulse pressure using multivariable linear regression models; and carotid artery lesions using multivariable log-binomial models. Models were adjusted for age, race/ethnicity, smoking, diabetes, body mass index, C-reactive protein and study site. Additional adjustment for nadir CD4+ T cell count did not change results appreciably, so was not included. We also examined whether the association between CMV IgG and vascular measures differed by HIV treatment and viremic status.

Results: Median age was 41 years, most participants were African-American (62%) or Latina (27%), and nearly half were smokers. Mean CMV IgG levels were 23.7 IU/mL among HIV-infected women and 17.6 IU/mL among HIV-uninfected women (P<0.01); 93% of HIV-infected and 90% of HIV-uninfected women had detectable IgG titers. Among HIV-infected women, higher CMV IgG was associated with two measures of arterial stiffness: decreased distensibility and increased Young's modulus. For each 10 IU/mL increase in CMV IgG, we observed a mean 0.7 decrease (in units of 10^{-6} x Newtons^{-1} x meters^{2}) (95% confidence interval [CI]: -1.2 to -0.2; P=0.01) in distensibility, and a mean 0.5 increase (10^{5} x Newtons x meters^{-2}) (95% CI: 0.1 to 0.8, P=0.01) in Young's modulus. Higher CMV IgG was associated with increased prevalence of carotid artery lesions among HIV-infected women who achieved HIV suppression on antiretroviral therapy, but not among viremic or untreated HIV-infected women. In treated aviremic women, each 10 IU/mL increase in CMV IgG was associated with a prevalence ratio for carotid artery lesions of 1.49 (95% CI: 1.05-2.28, P=0.03).

Conclusions: CMV antibody titers are increased in HIV-infected women relative to HIV-uninfected controls, and associated with increased subclinical cardiovascular disease. Our findings, and previous studies (Naeger DM et al., *PLoS One, 2010*), suggest that HIV-infected patients on effective antiretroviral therapy may be susceptible to develop vascular lesions in association with CMV co-infection. This association may be overshadowed by other vascular disease mechanisms in untreated or viremic HIV-infected women. While emerging evidence suggests that control of CMV may improve control of HIV (Hunt PW et al., *J Infect Dis, 2011*), our data suggest that treating CMV infection may also reduce cardiovascular risk in HIV-infected adults.

2nd International Workshop on HIV & Aging

27 – 28 October 2011, Baltimore, MD, USA

Abstracts

Poster Presentations

Abstract: P_01

Effect of aging on organ systems (renal, musculoskeletal, hepatic and endocrine)

Hypophosphatemia and albuminuria are associated with older age in HIV+ adults receiving antiretroviral therapy (ART)

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Introduction: Hypophosphatemia and albuminuria are observed frequently in HIV+ populations, possibly related to nephrotoxic effects of ART. We examined the frequency of and factors associated with hypophosphatemia and albuminuria among HIV+ adults in British Columbia (BC), where serum phosphate and urine albumin to creatinine ratio (UACR) are routinely monitored in ART-treated patients.

Materials and Methods: Serum phosphate results were obtained from the BC Centre for Excellence in HIV/AIDS Drug Treatment Programme (BCCfE DTP) database for all HIV+ adults who started ART between 01-August-1996 and 31-August-2009, and had >1 phosphate measurement <1 year before starting and >2 during follow-up. The analysis of hypophosphatemia incidence (defined as >2 consecutive phosphate measurements <0.8 mmol/L) included those with normal phosphate (>0.8 mmol/L) at pre-ART baseline. Few patients had UACR measured pre-ART; therefore, the analysis of albuminuria (defined as >1 UACR > 2.0 mg/mmol for males, >2.8 mg/mmol for females) was based on the most recent UACR results between 31-August-2009 and 31-August-2010 while on ART. Demographic information, HIV and ART history, and laboratory values relevant to HIV and renal function were obtained from the BCCfE DTP database. Cox proportional hazard regression was used to model time to incident hypophosphatemia. For cross-sectional UACR comparisons, Chi-square test and Fisher's exact test were used for categorical variables, Wilcoxon rank-sum test for continuous variables, and logistic regression for modeling.

Results: Among 499 patients tested for phosphate pre-ART, 473 (95%) were normal, 21 (4%) had mild hypophosphatemia (>0.65 to <0.80 mmol/L), and 5 (1%) had moderate hypophosphatemia (>0.32 to <0.65 mmol/L). Of the 473 with normal pre-ART phosphate, 398 (84%) were male and median age was 43 (interquartile range [IQR] 36, 50) years. Confirmed hypophosphatemia on ART occurred in 97 patients, for an incidence of 6.0 (95% confidence interval [CI] 4.8-7.2) events per 100 person-years. The multivariable model showed that confirmed hypophosphatemia was associated with older age (adjusted hazard ratio [AHR] 1.34 per 10 years, 95% CI 1.11 -1.62) and proportion of ART duration on abacavir (AHR 0.83 per 10%, 95% CI 0.75-0.91), zidovudine (AHR 0.87 per 10%, 95% CI 0.78 -0.99), and emtricitabine (AHR 0.89 per 10%, 95% CI 0.83-0.96). Of 782 ART-treated patients with UACR, 715 (91%) were male and median age was 47 (IQR 42, 54) years. UACR was normal in 596 (76%), 161 (21%) had microalbuminuria, and 25 (3%) had macroalbuminuria (UACR >30). The multivariable model showed that albuminuria was associated with older age (AHR 1.37 per 10 years, 95% CI 1.13-1.66), longer duration of ART (AHR 1.08 per year, 95% CI 1.02-1.14), lower eGFR (AHR 0.88 per 10 mL/min increase, 95% CI 0.80-0.96), and proportion of ART duration on atazanavir (AHR 1.06 per 10%, 95% CI 1.02-1.11).

Conclusions: Hypophosphatemia was observed in 5% of HIV patients before starting ART, and developed at a rate of 6.0 events/100 person-years on ART. Albuminuria was observed in 24% of patients on ART. Both renal abnormalities were significantly associated with older age. Use of abacavir was protective for hypophosphatemia and use of atazanavir was associated with albuminuria. Longer-term implications of these findings require further investigation.

Abstract: P_02

Effect of aging on organ systems (renal, musculoskeletal, hepatic and endocrine)

Reproductive dysfunction associated with different age groups among HIV-infected individuals in rural South India

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Background: There is limited data on reproductive dysfunction among HIV-infected men and women particularly in India. Studies have indicated that leptin may act as the critical link between adipose tissue and the reproductive system The objective was to find out the prevalence of sexual and menstrual dysfunction among HIV-infected men and women of different age groups, along with reproductive hormonal and leptin levels, as compared to non-infected controls.

Material and Methods: After informed consent, HIV-infected and non-infected individuals (age range: 18-45) were recruited from Namakkal district, TamilNadu, India. Details of menstrual history (women), and sexual function (men) were noted. Fasting leptin, follicle stimulating hormone (FSH), total testosterone and estradiol by ELISA was measured. BMI was calculated from measured height and weight. Statistical analysis: ANOVA, Pearson Chi-square.

Results: Among 297 subjects (45.8% men, 54.2% women), 146 were antiretroviral-naive, 79 were on antiretroviral therapy (ART) and 72 were HIV- negative. 36.03% were ≤ 30 years, 47.47% were 31-40 years, and 16.5% were >40 years. Mean BMI was significantly lower among the HIV-infected individuals (ART=22.06 ± 3.46, non-ART= 18.89 ± 3.5, HIV-ve= 26.39 ± 4.82 kg/m^2 ; p=0.00). HIV-infected women had a higher prevalence of long cycles (11.3%vs3.1%) and amenorrhea (5.7%vs3.5%) compared to HIV-negative women (p=0.067). A higher proportion of women ≤ 30 reporting long cycles (ART= 18.2%, non-ART=72.7%, HIV-ve=9.1%; p=0.533) and amenorrhea (ART= 20.0%, non-ART=80.0%, HIV-ve=nil; p=0.533) were HIV-infected. Also, ameorrheic women between 31-40 years were predominantly HIV-infected (ART= 33.3%, non-ART=33.3%, HIV-ve=33.3%; p=0.113). Among women >40, only antiretroviral-naïve women reported long cycles (p=0.066). Moreover, HIV-infected women ≤ 30 had significantly lower estradiol (ART=51.32 ± 39.6, non-ART= 36.52 ± 37.25, HIV-ve = 79.84 ± 50.0 pg/ml; p=0.003), higher FSH (ART=14.12 ± 15.04, non-ART= 19.33 ± 20.91, HIV-ve= 9.44 ± 6.54 mIU/ml; p=0.158) and significantly lower leptin (ART=12.42 ± 21.47, non-ART= 23.71 ± 34.94, HIV-ve= 61.73 ± 55.24 ng/ml; p=0.001). Regarding men, a higher proportion of HIV-infected men reported libido loss (45.6%vs16.7%; p=0.028) and erectile dysfunction (ED) (33.3%vs3.3%; p=0.001) than HIV-ve men. All the men ≤ 30 reporting loss of libido (ART= 40.0%, non-ART=60.0%; p=0.316) and ED (ART= 50.0%, non-ART=50.0%; p=0.082) were HIV-infected. A significantly higher proportion of men aged 31-40 reporting libido loss (ART= 23.1%, non-ART=73.1%, HIV-ve =3.8%; p=0.003) and ED (ART= 15.8%, non-ART=78.9%, HIV-ve =5.3%; p=0.002) were HIV-infected. All the men >40 reporting ED (ART= 37.5%, non-ART=62.5%; p=0.002) were HIV-infected. Also, HIV-infected men aged 31-40 years had lower testosterone (ART=4.74 ± 3.24, non-ART= 5.61 ± 3.13, HIV-ve = 6.86 ± 2.44 ng/ml; p=0.108), significantly higher FSH (ART=14.45 ± 19.4, non-ART= 16.94 ± 14.3, HIV-ve = 6.11 ± 3.71 mIU/ml; p=0.026) and significantly lower leptin (ART=3.3 ± 4.32, non-ART= 7.36 ± 6.16, HIV-ve= 29.5 ± 60.28 ng/ml; p=0.015).

Conclusions: Abnormal reproductive function including altered sex hormone levels normally associated with older age was seen in this rural HIV-infected population, even among those aged less than 30 years. Undernutrition and lower leptin levels may contribute to the reproductive abnormalities. Further studies may lead to a better understanding of the effect of HIV and its treatment on reproductive health and its sequelae.

Abstract: P_03

Effect of aging on organ systems (renal, musculoskeletal, hepatic and endocrine)

Chronic HIV Infection and Aging in NeuroAIDS (CHAIN): Gender Differences in Sexual Function

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Background: Presently, there are little available data evaluating the implications of aging with chronic HIV infection on sexual function. We report results of evaluations of sexual function in a well-characterized cohort of participants enrolled in a cross-sectional study of aging and HIV infection.

Methods: Participants were 20-40 years old (younger; n=21), and > 50 (older; n=20). 29 Males and 12 females underwent a history and physical examination; neuropsychological (NP) battery; measurement of activity using actigraph monitoring for 2 weeks; and surveys for depression, fatigue, loneliness and activities of daily living. Sexual satisfaction was assessed using validated questionnaires: the Sexual Health Questionnaire (SHQ), Female Sexual Function Index (FSFI) and Male Sexual Health Questionnaire (MSHQ).
Where applicable, a two-sample t-test or Wilcoxon rank sum test, was used to compare means for continuous variables between the two age groups. Exact Chi-Square tests were applied to compare proportions between the groups. Raw NP scores were standardized to z scores and adjusted for age and education, and a total z score was computed.

Results: The mean age of younger subjects was 31.5 years, 14 were men, 7 women, and white/black/Hispanic = 15/4/2. The mean age of older subjects was 56.5 years, 15 were men, 5 women and white/black/Hispanic = 13/5/2. There were no significant differences between groups for income, education, tobacco/substance abuse, CD4 count, viral load, depression, fatigue, loneliness or total activity levels. Older participants had more diagnoses (mean 2.2 vs 0.76, P=0.004), more concomitant medications (mean 4.3 vs 1.1, P=0.03), and a trend to lower NP scores (p=0.11). Younger women endorsed more sexual desire compared to older women (mean 3.9 vs 1.9, P=0.010). No differences were observed in other domains (arousal, lubrication, orgasm, satisfaction or pain). HIV-infected women had lower overall scores than uninfected, historical controls (mean 12.66 vs 19.2).
Younger men had higher scores on the erection scale than older men (mean 14.0 vs 9.5 P<0.001) but also more concerns about erectile performance (mean 4.85 vs 4.0 P=0.002). Erection scores correlated negatively with antiretroviral therapy (p=0.005), number of diagnoses (p=0.002), and concomitant medications (p=0.008). No differences were observed in other domains (ejaculation, satisfaction, desire). There were no differences between HIV-infected and uninfected, historical controls in erection, ejaculation or satisfaction (means 9.5 vs 8.3, 27.5 vs 16.9 and 22.7 vs 24.2 respectively). We did not observe correlations with sexual function and activity, NPZ score, fatigue or loneliness for men or women.

Conclusions: We observed gender differences in domains of sexual function among older and younger HIV-infected participants. Differences within gender groups indicated younger women participants had somewhat higher sexual desire, and younger men had better erectile function. Overall, HIV-infected women had lower scores than uninfected controls but HIV-infected men did not, suggesting HIV disease may have a stronger impact on sexual function for women than men. Further study is needed on the impact of HIV and aging on sexual function.

Abstract: P_04

Geriatrics and clinical care

Elderly condom use and perception: a barrier to family planning and mitigation of HIV/AIDS in high risk urban slums in Nigeria

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Background/Significance: As HIV/AIDS continues to pose a public health challenge Africa, the pandemic cut-across borders. It affects all the age groups including the geriatrics, despite engagement in risky sexual activities which increases HIV/AIDS infection. However, limited attention is paid to this population in mitigating the pandemic. This study therefore examined condom-use and perceived HIV/AIDS infection among geriatrics in Nigeria.

Methodology: The study was cross-sectional in design. A multi-stage sampling procedure was used to select 400-geriatrics. Pre-tested questionnaire developed, using information obtained from 10 Focus Group Discussion (FGD), was used to collect information. FGD data were analyzed thematically, while questionnaire data were analyzed using descriptive and statistically.

Findings: Twenty-five percent of the participants had extra-marital sex since they attained elderly age. However, among this subgroup that had extra-marital sex, few (6.8%) used a condom. More males (5.3%) than females (1.5%) used condom during the last extramarital sex. Low level of condom-use was attributed to condom not worthwhile (34.5%) and opinion (50.0%) condom not made for the elderly. Moreover, FGD participants viewed sex could not lead to pregnancy and majority (60.3%) posited patronizing traditional healers and few (10.3%) use of herbs/concussion could prevent HIV/AIDS. Similarly, non-condom use was due to confidence in traditional herbs, perceived to protect against STIs including HIV/AIDS.

Conclusion: Engagement in risky activities among elderly is a growing HIV/AIDS challenge. Condom-use is misconstrued probably due to knowledge gap. Without urgent measures to enable them protect themselves, development efforts will be in jeopardy. Investing in geriatric SRH is cost-effective intervention in mitigating HIV/AIDS pandemic.

Abstract: P_05

Geriatrics and clinical care

Eliciting cognitive complaints in non-demented HIV individuals: what to ask, who to ask

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Background: Although there is consensus in the HIV medical community that identifying neuropsychological impairment should be an integral part of on-going care, clear guidelines on how to best elicit information regarding cognitive-behavioural symptoms are lacking. Which specific questions, asked of a patient or an informant, are best at eliciting the difficulties experienced by HIV individuals in their daily life?

Objectives: The objectives of this study were to estimate the extent to which patient and informant responses to the individual items of the Multiple Sclerosis Neurological Questionnaire (MSNQ) link to a single construct of cognitive-behavioural symptoms and to estimate the degree of concordance between patient- and informant- reports on this construct.

Material & Methods: A convenience sample of persons aged 18-70 was recruited from individuals with HIV infection at sequential visits to the Immunodeficiency Clinic of the McGill University Health Centre. Exclusion criteria were overt dementia (MMSE < 23 or MoCA < 20),

history of neurological event, use of psychoactive medication in doses likely to affect cognition, and current substance abuse. The protocol was approved by the institutional ethics board and all participants provided informed consent. Cognitive complaints were documented using the 15-item MSNQ. If available, an informant completed the informant version of the MNSQ. Both sets of responses were combined; the resulting 30 items were Rasch-analyzed in RUMM2020 software using the partial-credit model to evaluate fit to the hypothesized unidimensional linear latent construct.

Results: 53 patients and 25 informants participated. Patients, predominantly men (92%), were relatively well educated, had a long history of HIV infection (mean: 13.9 ± 6.7 yr) and were successfully treated with HAART. Several items had to be rescored as the distribution of the response options did not follow a logical sequence based on the latent trait. Out of a 150 possible response options, 95 were retained. Two patient-reported items (difficulty controlling impulses, focusing too much on own interest) did not fit the model. Overall, patients discriminated a greater number of levels of symptom severity than did informants, with items spanning the full range of the latent construct from -3.7 to 3.3 logits, whereas informant responses clustered around the mean between -1.6 to 2.2 logits. Patients endorsed greater severity than informants on items 'missing the point of what someone is trying to say' and 'being slow when trying to solve problem'. Those last two questions, plus 'needing to have instructions repeated' were shown to be particularly useful in determining the level of reported cognitive symptoms; they would constitute useful screening questions.

Abstract: P_06

Geriatrics and clinical care

HIV-Infected and non HIV-Infected Elderly Patients: do their drug interactions differ?

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Introduction/Background: Elderly HIV-infected patients may present particularities on both disease evolution and morbidity, as compared to younger patients. Moreover, elderly patients are more likely to take numerous medications due to their age-related condition. VISAGE is a French multidisciplinary study group focusing on elderly HIV-infected patients. Our study "VISAGE 2" aimed to compare nature and number of drug interactions (DI) between HIV-infected (pHIV) and non-HIV infected elderly patients (non-pHIV) on their usual drugs other than antiretrovirals.

Material & Methods **:** This 6-month prospective study carried in 2010 had involved non-HIV infected patients aging more than 60 years, and was a sequel of a former 6-month prospective study involving pHIV in 2009 and aging more than 60 years at the time of the study ("VISAGE 1" study). pHIV were mostly cared for in specialized hospital wards and in offices of physician members of HIV-dedicated city-hospital networks, while non- pHIV were mostly cared in offices. Patients were to fill an anonymous self-questionnaire for reporting their diseases and drugs or products regularly taken. Analysis of DI relied on the French drug agency (Afssaps) thesaurus by using the tool available on the website www.theriaque.org.

Results: 236 pHIV and 120 non-pHIV filled the questionnaires. For pHIV and non-pHIV: women accounted for 20% and 56% ($p<10E^{-5}$). Number of more than 65 years was 125 (53%) and of non-pHIV 97 (81%) ($p<10E^{-5}$) and mean age was 67 and 71 years, respectively.

Main reported diseases and symptoms for non-pHIV were cardiac (84%), arthritis and osteoporosis (61%), pain (36%). 220 pHIV (93%) reported treatment other than ARV, (mean number of 4.9 drugs per patient) while 119 non-pHIV (99%) did (mean number of 5.6 drugs per patient) ($p<.05$). The 5 most frequently non-ARV drugs used by the 220 pHIV were: paracetamol (29%), lysine acetyl salicylate (14%), bromazepam (10%), rosuvastatin (10%), and clopidogrel (8%). The 5 most frequently drugs used by the 119 non-pHIV were: paracetamol (53%), irbesartan (15%), hydrochlorothiazide (13%), metformine (13%), and clopidogrel (9%). Clinically relevant DI occurred in 95 pHIV (40%) (150 DI, mean number of 1.6 DI per patient) and in 49 non-pHIV (48%) (75 DI, mean number of 1.5 DI per patient) ($p>.05$). Numbers of "contra-indicated" DI were 5 in pHIV (concerned ARV/non-ARV drugs associations: ritonavir + alfusozine and protease inhibitor + simvastatin with risk of increased plasma levels of both products and of their respective side effects), and 1 in non-pHIV (concerned spironolactone + potassium chloride with risk of hyperkaliema). Other levels of DI were: "take into account": 61 (41%) in pHIV and 36 (48%) in non-pHIV; "use with caution": 51 (34%) and 29 (39%), respectively; "not recommended": 31 (21%) and 9 (12%), respectively (ns).

Conclusions: In this study, pHIV did not report more DI despite ARV treatment which is more likely to induce numerous adverse events and DI. Treatment was comparable between pHIV and non-pHIV. This supports our hypothesis raised in a previous study (VISAGE 1, cf. abstract) of a monitoring of HIV patients with greater attention to the prescription of non-ARV treatments, the potential for interaction and the overall adherence.

Abstract: P_07

Geriatrics and clinical care

Frailty among HIV-infected and uninfected individuals in Cape Town, South Africa

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Background: Frailty refers to decreased physiological reserve characterised by multiple pathologies, low physical activity and slow motor performance. Although frailty is typically viewed as a geriatric syndrome, HIV infection has also been reported to be associated with premature development of frailty. In sub-Saharan Africa HIV-infected (HIV+) individuals typically present late with advanced immunodeficiency, and data on HIV-related frailty are limited The aim of this study is to compare rates of frailty within a cohort of HIV+ patients attending an antiretroviral treatment (ART) service and an age- and gender-matched HIV- control group in Cape Town, South Africa. A secondary aim is to assess the impact of ART on frailty among HIV-infected individuals.

Materials and methods: Cross-sectional study of two clinic-based cohorts representing HIV+ and confirmed HIV- individuals, frequency matched by age and sex, and living in similar socioeconomic conditions in a township community. Adults greater than 30 years were enrolled between April and September 2011. Frailty was defined as ≥3 of 5 criteria: weight loss, low physical activity, exhaustion, weak grip strength and slow walking time which divided participants into 'frail' and 'non-frail' groups. Explanatory variables included socioeconomic factors, medical history and HIV infection characteristics where applicable. Independent predictors of frailty were evaluated using multiple logistic regression.

Results: 178 participants were evaluated (79 HIV+/79 HIV-). Groups were similar with respect to age and gender (HIV+ group: median age 41 years, interquartile range [IQR] 36-39, 25.3% male; HIV- group: median age 39 years, IQR 33-50, 31.7% male, p=0.4 for age). 24.4% of the HIV- group were frail compared with 14.9% in the HIV+ group (p=0.14). Among the uninfected group, frailty was only associated with female gender (p=0.01), and increasing age (p_{trend}=0.001) and a greater frequency of co-morbid conditions (63.6% vs. 15.9%, p=0.001). Frailty was not associated with alcohol use, smoking or illicit drug use in either group. In the HIV+ cohort frailty was not associated with gender or age but was associated with prevalent tuberculosis (15.8% in frail vs 1.7% in non-frail persons, p=0.01). Frailty was higher among those HIV+ individuals not yet receiving ART (31.6% vs. 5.2%, p=0.002). However, in participants receiving ART, frailty was associated with a longer duration of treatment (mean duration 69.1 months vs. 50.8 months, p=0.04) but was not associated with nadir/current CD4 cell count or viral load. The only socioeconomic predictor of frailty in the HIV+ group was having completed less education (31.6% vs. 10.2% with no high school education, p=0.02). Independent predictors of frailty in the HIV+ cohort included being HAART-naïve (odds ratio [OR] 8.8, p=0.006) and low education level (OR 4.02, p=0.04).

Conclusions: The prevalence of frailty is high in both HIV-infected and uninfected groups compared to data from Western populations. Frailty within the uninfected population is related to increasing chronological age, and the presence of co-morbid conditions, consistent with reports from other populations. Frailty within the HIV-infected group was not related to age- or gender, but was increased in those with lower educational level (likely indicative of lower socioeconomic status), and was substantially lower in those receiving ART.

Abstract: P_08

Geriatrics and clinical care

Impact of Age on Mood States in Persons Living with HIV Infection

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Background: While prevalence of major depression decreases with age among persons infected with HIV, the prevalence and impact of subsyndromal depressive symptoms and negative mood states have not been studied in this population. To address this topic, we compared older (aged 50 or above) persons with HIV to a sample of younger persons (aged 49 or below) with HIV to assess of the relationship of age to mood states in persons living with HIV infection.

Methods: The participants were 124 HIV-infected persons enrolled at the UCSD HIV Neurobehavioral Research Program (HNRP), who were recruited from the community or HIV clinics in San Diego, using flyers or newspaper advertisements. All participants underwent comprehensive laboratory, neuromedical, neurocognitive, and psychiatric assessments, including the Profile of Mood States (POMS). The POMS is a self-report questionnaire measuring mood states (i.e., depression, anxiety, fatigue, anger, and vigor) over the preceding seven days. The measure consists of 65 adjectives (e.g. hopeless, annoyed, sluggish) or short phrases (e.g. sorry for things done, ready to fight), which the patient rates on a five-point Likert-type scale ranging from 0 (not at all) to 4 (extremely). We applied logarithmic conversion to POMS total and subscale scores to correct for skewness and compared older participants to younger subjects using ANOVA and Chi-square tests, and identified predictors of mood states using linear regression.

Results: Our sample comprised 37 older and 87 younger adults. The older group included significantly more men (89% vs. 75%) but the groups did not differ on other socio-demographic variables (race/ethnicity and education) or HIV

severity indicators (CD4 count, CD4 nadir, or plasma viral load), cardiovascular risk, Hepatitis C status, or neurocognitive composite scores. The older group had lower mean scores on POMS total, as well as the Tension/Anxiety and Anger/Hostility subscales ($p < .05$). There were no differences between the groups on any other POMS subscales. We conducted separate follow-up linear regressions to assess predictors of POMS total, Tension/Anxiety, and Anger/Hostility scales. Age was not associated with POMS total or Tension/Anxiety (ps > .10) in these models; however, older age was the sole significant predictor of lower Anger/Hostility scores (ß=-.249, p=0.010) in the final model. The whole model, which also included neurocognitive composite scores, HIV severity indicators, and cardiovascular risk measures explained a relatively small proportion of variance (adjusted R2 = 0.139, p=0.039).

Conclusions: Our findings suggest that older adults with HIV experience less symptoms of anger, but not other emotional symptoms such as anxiety and depression, than younger HIV + adults. The results differ somewhat from prior studies that reported less depression in older HIV+ and non-HIV samples. Whether this means that only syndromal depression lessens with age, whereas milder symptoms are similar in young and old will need to be determined in larger longitudinal studies that include a wider breadth of aging-related variables to explain a greater proportion of the variance in anger and other mood state scores.

Abstract: P_09

Geriatrics and clinical care

SWIFT: Switching from Lamivudine/Abacavir to Emtricitabine/Tenofovir Improved Lipids While Maintaining Virologic Suppression in Older HIV Subjects

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Background: In prior treatment naïve and experienced studies, use of FTC/TDF has been associated with a favorable lipid profile and has not been associated with increased MI risk. However, there are limited data on the impact of switching from 3TC/ABC to FTC/TDF, particularly in older HIV+ subjects.

Methods: Prospective, multicenter, randomized 48 week study to evaluate the safety and efficacy of a strategy of switching subjects receiving 3TC/ABC + PI/r with HIV RNA < 200c/mL ≥ 3 months to continue 3TC/ABC or switch to FTC/TDF, with PI/r unchanged. Subjects were stratified by PI/r (LPV/r vs. other) and comorbidities (CV disease, DM, hyperlipidemias). Primary endpoint was time to loss of virologic response (TLOVR) (virologic failure - HIV RNA>200 c/mL, premature discontinuation, or ARV modification = failure). Fasting lipid profile and 10-year Framingham scores were evaluated though Week 48. This is a sub analysis by age < 50 or > 50 years.

Results: A total of 311 subjects were treated (FTC/TDF n=155, 3TC/ABC n=156), 198 (64%) were <50 and 113 (36%) were > 50 years. Of those ≥ 50 years (n=113), 53% were randomized to FTC/TDF and 47% continued 3TC/ABC, 84% were male, 29% African Americans, median age

(range) 54 (50-75), 58% taking lipid-lowering agents, and 31% on LPV/r and 87% with pre-specified co-morbidities. Overall, switching to FTC/TDF was non-inferior to 3TC/ABC by TLOVR (86% vs. 83%) through Week 48. In the subjects ≥50, FTC/TDF remained non-inferior to 3TC/ABC by TLOVR (difference of 4.7%; 95% CI [-7.6%, 17.8%]) and fewer subjects on FTC/TDF vs. 3TC/ABC experienced VF (0 vs. 4; p=0.037). In the subjects ≥50, early discontinuation rates were lower than those <50 (8.8 vs.12.1%), with no difference between the treatment arms. AEs related to study drug were less common in subjects ≥50 (5.3% v. 8.1%). Grade 3 or 4 AEs were more common in subjects ≥ 50 but less common in these subjects on FTC/TDF (8.3% vs.17%). Mean eGFR declined in both arms at Week 48, with -1.9 mL/min on 3TC/ABC and -8.3 mL/min on FTC/TDF (p=0.007 between arms). There were no differences in renal discontinuations between the treatment arms. Compared to baseline levels, the median changes in Week 48 lipid parameters for subjects ≥50 were: total cholesterol (-11; p=0.030 vs. -19 mg/dL; p< 0.001), triglycerides (-12; p=0.42 vs. -42 mg/dL; p< 0.001), and the TC/HDL ratio (-0.3; p=0.063 vs. -0.3; p= 0.028) for those remaining on 3TC/ABC versus those who switched to FTC/TDF respectively. Median (SD) change at Week 48 in 10-year Framingham scores were -1.1 (5.6; p=0.18) and -2.1 (5.5; p=0.008) for the continue 3TC/ABC vs. FTC/TDF treatment arms respectively.

Conclusions: In older HIV+ population on PI/r, switching subjects from 3TC/ABC to FTC/TDF maintained virologic suppression and improved lipid parameters and Framingham scores. Declines in eGFR were seen in both arms, higher in the FTC/TDF, with no difference in renal AEs.

Study was performed in close collaboration with Gilead Sciences

Abstract: P_10

Geriatrics and clinical care

Assessing the Quality of Life of Long-Term Diagnosed HIV-Infected Subjects

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Background: Successful aging is based not only on the absence of illness but also on the achievement of an adequate quality of life, understanding this as the concept of wellness. Little is known about the quality of life of long-term diagnosed patients aging with HIV infection.

Material & Methods: Cross-sectional study of 40 HIV-1 infected subjects (20 men and 20 women) who received their diagnosis of HIV infection at least 15 years ago. Data collected included demographic and clinical variables. Quality of life was assessed with Nottingham Health Profile (NHP) questionnaire, which is composed of 2 sections. The first section has 38 statements that assess 6 different dimensions of normal living: energy, pain, emotional reactions, sleep, social isolation and physical mobility. Scores for each dimension can range from 0 "no problems" to 100 "all problems listed are present". The second section is composed of 7 single statements about 7 areas of daily life: work, looking after the home, social life, relationships at home, sex life, interests and hobbies, and the ability to take holidays. Patients are asked to answer whether their health causes problems in any of these areas. Statistical summaries were prepared for the main variables. Continuous variables were described as median (IQR) and compared by using non parametric tests. Categorical variables were assessed by percentages (absolute frequencies). χ^2-test or Fisher exact test, as appropriate, were performed to compare men and women.

Results: The demographic and clinical characteristics of the sample were: mean (SD) age: 50 (46-52), years since HIV-1 infection: 20 (16-24), years on ART: 16 (12-18), nadir CD4: 156 (68-253) cell/mm^3, current CD4: 527 (364-633) cell/mm^3, CV<25 copies in 39 subjects. Forty-three percent of subjects had a stable partner and 51% were retirees. Quality of life scores were: energy: 100 (0-100), pain: 40 (10-80), emotional reactions: 53 (25-76), sleep: 50 (22-77), social isolation: 41 (19-64) and physical mobility: 21 (0-32). Work was affected in 75% of subjects, looking after the home in 67%, social life in 65%, relationships at home in 42%, sex life in 62%, interests and hobbies in 42% and holidays in 35%. Women reported higher pain (p=0.04) and higher affectation in looking after the home (p=0.01), social life (p=0.004), relationships at home (p=0.02) and interests and hobbies (p=0.02).

Conclusions: Despite the good immune situation observed, quality of life was poor in this group of long-term diagnosed HIV-infected patients, especially the dimension of energy and the areas of work, looking after the home, social life and sex. Quality of life affected more areas of daily life in women than in men

Abstract: P_11

Geriatrics and clinical care

Prevalence of HIV testing among middle and older-aged adult Floridians

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Objective: Testing is important for the prevention of the spread of the Human Immunodeficiency virus among middle and older adults. The aim of this study was to identify the prevalence of HIV testing among adults 45-64 years of age in Florida, and to determine the difference in the incidence of testing between 2002 and 2007.

Methods: Secondary data analysis conducted of the Florida Behavioral Risk Factor Surveillance System (BRFSS) survey utilizing the Community Health Assessment Resource Tool (CHART). The BRFSS assesses personal health behaviors contributing to morbidity and mortality. Analysis examined the State-wide prevalence of HIV testing of adults between the ages of 45-64 at two points in time; 2002 and 2007.

Results: Year 2007 prevalence of HIV testing was 35.9 (95% CI: 34.2-37.7) for adults ages 45-64 compared to HIV testing in 2002; 33.2 (95% CI: 31.2-35.4). Results revealed a 2.7% increase. A decrease occurred in the number of adults ages 45-64 who had tested in the past 12 months for data comparing prevalence in year 2002, 12.6 (95% CI: 11.1-14.3) with testing results in 2007; 10.8 (95% CI: 9.6-12.1).

Conclusion: A need exists for on-going age, gender, and ethnic/racial group appropriate, health education and health promotion efforts to increase HIV testing and to promote disease prevention among middle and older aged adults; a population that may perceive itself at low-risk for HIV infection.

Abstract: P_12

Immunology

Distorted virus-specific T-cell function and phenotype in the ageing HIV-1+ cohort

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Background: HIV-1 infection in older adults is associated with faster disease progression. Average patient age has risen since the introduction of HAART, so delineating the compounded effects of age and HIV-1 on rate of progression and potential immune reconstitution is relevant for future therapeutics.

Materials and Methods: Functional T-cell responses to HIV-1 Gag p24 and CMV in 58 HIV-1$^+$ HAART-treated individuals were assessed by IFN-γ and IL-2 ELISpot, and proliferation assays. Median age was 48 years (range 29-71) and time since HIV-1$^+$ diagnosis 14 years (range 1-26). Duration of ART ranged from 0.5-26 years (median 14). Flow cytometry investigated expression of cell-surface markers associated with T-cell differentiation (CD27/CD28), activation (HLA-DR/CD38), co-stimulation/inhibition (CD28/CTLA-4), senescence (CD57) and exhaustion (PD-1). Data were analysed using univariate and multivariable regression models incorporating patient age, time since HIV-1$^+$ diagnosis and ART duration.

Results: There is evidence that age is an independent predictive factor of the proliferative ($p=0.0637$, $r^2=0.2008$) and IL-2-secreting ($p=0.0622$, $r^2=0.3652$) responses to HIV-1 Gag p24 peptides (Gag_{20}), when adjusted for time since HIV-1$^+$ diagnosis and ART duration. As patients age, proliferation and IL-2-production in response to Gag_{20} decline, with patient age explaining 20% of variation in proliferation, and 37% in IL-2 response. Time since HIV-1$^+$ diagnosis is a significant independent predictive factor of the increase in IFN-γ response to Gag_{20} ($p=0.0295$, $r^2=0.1706$) and rise in IL-2 production to CMV ($p=0.0478$, $r^2=0.4301$) when adjusted for patient age and ART duration. Seventeen percent of variation in IFN-γ production to Gag_{20} and 43% of variation in IL-2 production to CMV can be explained by length of HIV-1$^+$ infection. CD57 expression on CD8 T cells increased significantly with age ($p=0.0470$, $r^2=0.0698$). The % expression of co-stimulatory CD28 and proportion of cells at the early stage of differentiation within the CD8 T-cell compartment exhibited significant decline with advancing age ($p=0.0364$, $r^2=0.0758$ and $p=0.0012$, $r^2=0.1713$ respectively). There was a significant decline in CD38 expression on CD4 T cells as ART duration increased ($p=0.0277$, $r^2=0.0836$). CD4 T cells at the intermediate stage of differentiation increased significantly with increasing patient age, time since HIV-1$^+$ diagnosis and ART duration (all $p<0.004$, all $r^2>0.14$), and there was a significant decrease in the CD4 T-cell early subset as ART duration increased ($p=0.0392$, $r^2=0.0738$).

Conclusions: Age contributes towards decline in proliferative and IL-2 responses to HIV-1 Gag, and time since HIV-1$^+$ diagnosis is a significant independent predictive factor of the increase in IFN-γ response. Senescence of CD8 T cells increased significantly with age, whilst CD8 T cells expressing co-stimulatory surface molecules, and those at an early stage of differentiation significantly decreased. The proportion of early CD4 T cells significantly declined with advancing age, length of HIV-1 infection and ART duration. Expression of the activation marker CD38 also significantly declined as ART duration increased. Although patient age significantly contributes to changes in T-cell function and phenotype, ART duration and time since HIV-1$^+$ diagnosis are important explanatory variables to consider when analysing the ageing HIV-1$^+$ cohort.

Abstract: P_13

Immunology

Perceived Stress is a Strong Predictor of Elevated Levels of IL-6 in HIV-Infected, cART-treated Individuals

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Background: In recent studies, elevated levels of inflammation biomarker interleukin 6 (IL-6) have been associated with an increased risk of mortality in HIV-1 infected subjects despite effective cART. Psychosocial stress hastens the onset and course of inflammatory disorders but the association between stress and increase of circulating IL-6 levels in HIV-1 infected subjects with prolonged viral suppression remains unknown.

Material & Methods: Cross-sectional study of 50 HIV-1 infected subjects with confirmed diagnosis of HIV infection in the last 1 to 8 years, continual and effective cART for at least 1 year, and nadir CD4 cell count >250 cells/mm^3. Data collected included clinical variables (time under cART, antiretroviral drugs, CD4 and CD8 cell count, ratio CD4/CD8, HBV/HCV coinfection) and habits (sleep quality, physical exercise, healthy diet, adherence to cART, sexual risk practice, smoking, use of alcohol, illicit drugs) to control their possible contribution in the relationship between stress and IL-6. Psychological stress was assessed by the Perceived Stress Scale (PSS-10), anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS) and plasma IL-6 levels determined by a commercial ELISA assay (Quantikine Human IL-6 Immunoassay; R&D systems). Univariate and multivariate regression analyses for left-censored data using maximum likelihood estimation were used to determine predictors of IL-6.

Results: The demographic and clinical characteristics of the sample were: male (88%), mean (SD) age: 38.4 (9.2), time since HIV-1 infection: 4.33 (2.5) years, CD4: 738.26 (233.8) cell/mm^3, CD8: 846 (309.3) cell/mm^3, ratio CD4/CD8: 2.90 (13.7), years on cART: 3.53 (2.3), 62% on a NNRTI-based therapy, 24% coinfected with HBV and 8% with HCV. Mean (SD) IL-6 was 8.8 (3.7) pg/ml, PSS-10 was 16.66 (7.6), and HADS was 11.3 (6.6). In the univariate analysis, PSS-10 (coef: 0.49; SD: 0.05; p-value: 5.82e-17), HADS (0.37; 0.08; 2.12e-05), and healthy diet (-2.94; 1.38; 3.39e-02) were associated with higher levels of IL-6. In the multivariate model, only PSS-10 remained strongly associated with levels of circulating IL-6 (R^2: 59%; p-value: 5.82e-17).

Conclusions: This study suggests that psychological stress is associated with increased levels of circulating IL-6 in HIV-1 infected subjects with viral suppression. In the light of recent findings associating IL-6 levels with increased non-AIDS-related morbidity and mortality while on cART, the data urgently calls for more extensive studies in long-term treated HIV-infected individuals.

Abstract: P_14

Immunology

AntiViral-HyperActivation Limiting Therapeutics reduce both HIV and immune hyperactivation restoring immune system damage. A Clinical Proof of Concept

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Background: Chronic hyperactivation over the course of HIV disease exhausts the immune system and causes premature aging. Although HAART can maximally suppress HIV viral load, T cell activation and proliferation markers do not return to non-HIV-infected values, end-organ diseases occur more rapidly and more frequently, and life expectancy remains shorter in HIV-infected compared to uninfected individuals. We examined whether immune system hyperactivation is affected by a newly-developed class of anti-HIV drugs called AntiViral-HyperActivation Limiting Therapeutics (AV-HALTs) exhibiting dual activities: suppressing HIV replication and limiting excessive T cell proliferation.

Methods: Blood samples from 32 ART-naïve subjects receiving VS411, a fixed-dose AV-HALT combination of an antiviral drug (low-dose, slow-release 2',3'-dideoxyinosine) and an anti-proliferative drug (low-dose hydroxycarbamide), were analyzed in a multinational 4-week Phase 2a, double-blinded, placebo-controlled study using 10-color flow cytometry including T cell subsetting, activation and proliferation markers. Two-tailed paired t-test, non-parametric Wilcoxon test, and Pearson correlation were employed for statistical analysis.

Results: After 28 days of AV-HALT therapy, the median HIV RNA decrease was 1.47 log10 with only two of the 32 subjects reaching <50 copies/mL; median CD4+T cell increase was +108 cells/mm3. Despite incomplete viral load suppression, the median CD38+/HLA-DR+ co-

expression in CD4+ and CD8+ cells was significantly reduced by 28.9% and 24,4%, respectively (P values <.005); Ki-67 (proliferation marker) and PD-1 (exhaustion marker) expression in the CD3+ subset was also reduced by 29.0% and 26.1%, respectively (P values <.005). Naïve cells significantly increased, with the highest amount of baseline activation significantly correlating with the largest increase in total naïve cells (r^2 = 0.232, P<.005) and decrease in proliferating naïve cells (r^2 = 0.162, P<.01). A predictive, negative correlation between the percentage proliferating (Ki-67+) CD3+, CD8+, and CD4+T cells at baseline and HIV viral load changes after 28 days of AV-HALT therapy was also found (r^2 =0.272, P<.005; r^2 =0.189, P<.05; and r^2 =0.21, P<.05, respectively).

Conclusion: In addition to reducing HIV replication, a rapid, significant decrease of several activation markers in both CD4+ and CD8+ T cell subsets was achieved without completely suppressing viral replication, following only 28 days of AV-HALT therapy in ART-naïve subjects. Such decrease was comparable to that achieved after months/years of fully suppressive HAART. A high degree of cell proliferation before therapy predicted a poor antiviral response. While the memory cell compartment was minimally affected, the naïve T cell compartment was replenished, proportional to the extent of T cell activation before therapy. These results suggest that immune system hyperactivation driving disease progression can be specifically, rapidly and effectively reduced by AV-HALTs, resulting in a proportional restoration of the immune system damage.

Abstract: P_16

Immunology

Recovery of CD4 T-cells in older versus younger HIV patients with prolonged virologic suppression and low baseline CD4 T-cell counts

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Background: Chronically infected HIV patients (pts) and recent sero-converters are getting older. It is uncertain how this will affect management strategies. Accelerated immunosenescence may contribute to the more rapid clinical decline occurring in older untreated pts. Although virologic response to HAART is similar in older pts there is no consensus regarding age-dependent immunologic recovery on HAART, particularly in pts with low baseline CD4 counts. We compared changes in CD4 T-cell parameters in older vs younger pts in a cohort of chronically virologically suppressed pts on long-term HAART.

Materials & Methods: We analyzed 180 pts followed prospectively at the Immunodeficiency Treatment Center who had a well-defined start date of first HAART, remained on the same regimen or changed for non-virologic failure reasons, and always maintained an undetectable HIV viral load (VL) (50 copies HIV RNA/ml) for 5 years after the initial undetectable HIV VL. Subjects with an initial absolute CD4 count of <200/mm^3 were stratified into those >50 and <50 years old. Baseline clinical, immuno-virologic and treatment characteristics at time of first HAART were compared using parametric and nonparametric T-tests and proportions were compared by Chi-square analysis. Changes in absolute CD4 counts over time were determined by linear regression and were compared between older and younger subjects.

Results: There were 41 (23 %) pts with baseline CD4 cells <200; 16 of these pts (39 %) were > 50 yr old (mean age=57 ± 5) and 25 (61 %) were < 50 yr old (mean age =37 ± 6), p< 0.0001. The

median year of first HAART was 1997 in both groups. The median time from beginning HAART to first undetectable HIV VL was similar in both groups (12 months vs 7 months, p=NS). Proportions of younger vs. older pts on PI vs. non-PI based HAART were similar (P=NS).Baseline values for pts <50 vs >50 yr old were: absolute CD4+ cells (no./mm^3)-88 vs 104 (p=NS); % CD4+ cells -9 vs 10 (p=NS); % CD8+ cells-63 vs 65 (p=NS); % CD3+ cells-73 vs 76 (p=NS); CD4/CD8 ratio-0.15 vs 0.16 (p=NS); log_{10} HIV RNA-5.07 vs 5.00 (P=NS). The rate of change of CD4 cells in pts <50 vs >50 yr old was 38 ± 5 cells /yr vs 36 ± 12 cells /yr (p=NS). This represents a mean increase in CD4 cells above baseline in the <50 vs >50 yr old pts of approximately 190 vs 180 cells respectively during the follow-up period, leading to a mean CD4 count in the <50 vs > 50 yr old pts of 280 vs 285 after 5 yr of virologically effective HAART.

Conclusions: The increase in CD4 T-cells was similar in older vs younger pts with severe immunosuppression and comparable immune status markers at baseline who maintained effective virologic control over an extended follow-up period. The increase in CD4 cells in both groups was modest and reached <500/mm^3 at 5 yrs, a level associated with increased risk of serious non-AIDS events. Older and younger pts showed similar increase in CD4 cells in response to HAART.

Abstract: P_17

Metabolic/ cardiovascular complications

A study on highly active anti retroviral therapy – associated metabolic syndrome and cardiovasucular risk

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Background: The high global prevalence of human immunodeficiency virus (HIV) infection has been associated with high morbidity and mortality. The introduction of highly active antiretroviral therapy (HAART) has significantly modified the course of human immunodeficiency virus (HIV) disease, with longer survival and improved quality of life of HIV-infected patients. The clinical management of HIV-infected individuals is based on highly active antiretroviral combination therapy, which provides significant clinical benefit in most patients, but causes in a high proportion of them a metabolic syndrome and cardio vascular risk.

Methods: However, HAART regimens, especially those including protease inhibitors, have been shown to cause in a high proportion of HIV-infected patients a metabolic syndrome (lipodystrophy / lipoatrophy, dyslipidemia, type 2 diabetes mellitus, insulin resistance) that may be associated with an increased risk of cardiovascular disease (coronary artery disease and stroke). To analyze this, the- Blood donors Organisation for Social Service (BOSS) and its AIDS Branch -Centre for Information, Prevention and Counselling on AIDS (CIPCA), A Registered Charitable Non-Govt. Voluntary Community Based Organisation has conducted a two years stratified random sample study among 500 Persons Living with HIV/AIDS with HAART regimens in Andhra Pradesh state from Jan 2009 to December 2010 and results were analyzed by using advanced statistical methods.

Results: Among 500 PLWAs surviving with HAART 210(42%) patients have developed metabolic complications of HIV infection including increased predisposition to atherosclerotic disease. Among 210 – 96 (46%)are with hypercholesterolemia, hypertriglyceridaemia, low plasma HDL-cholesterol only and remaining 114 (54%) are with above complications and as well as alterations in other cardiovascular risk factors including inflammatory markers, clotting factors, homocysteine, apolipoproteins, lipoprotein (a), oxidative stress and non-esterified fatty acids. This study explores metabolic abnormalities associated with increased cardiovascular risk that occurs in HIV infection before and after antiretroviral therapy. The laboratory investigations, clinical management of HIV-associated dyslipidaemia and lipodystrophy closely observed in these PLWAs

Conclusions: A careful metabolic and cardiovascular evaluation in the course of HIV disease can identify both metabolic and cardiac complications early enough to treat. All HIV-

infected patients who are either candidates to antiretroviral therapy or who are already under treatment should undergo an assessment that includes the evaluation of the metabolic and cardiovascular risk with the available guidelines and the interactions between antiretroviral and drugs commonly used to treat these diseases. The management of lipid abnormalities, diabetes and hypertension should be encouraged in all HIV patients following guidelines for the general population. The life style changes, together with pharmacological intervention, should be advised when needed and potential drug interactions with ARV agents must be taken in to account.

Abstract: P-18

Metabolic/ cardiovascular complications

Age-specific prevalence of lipodystrophy among HIV positive individuals on ART in South India

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Background: Lipodystrophy has been increasingly observed in HIV infected individuals on Antiretroviral Therapy (ART) in India. The objective of this study was to compare the prevalence of lipodystrophy in different age group among individuals on ART in South India.

Material and Methods: In this cross sectional study, consenting HIV-infected patients on ART, visiting Namakkal District Head Quarters Hospital, Tamil Nadu, India, were recruited from February-April 2009. They were on generic first-line fixed dose combinations of ART, provided free of charge under the national program. Sociodemographics, anthropometric measurement, details of ART regimens and duration of treatment were recorded. Patients' self-perception of lipodystrophy was obtained using standardized questionnaires and clinically confirmed by the physician at the ART center. Statistical analysis included chi-square test and t-test.

Results: There were 145 HIV-infected subjects (46.9% males, 53.1 % females) receiving ART for a mean 29.4 months with 40.6% on zidovudine based regimen and 59.4% on stavudine regimen. Mean age of the subjects was 33.92 ±7.23 years and mean body mass index was 22.26± 4.46 kg/m2. Among the different age groups, 6.9% (n=10) were <25 years, 41.4% (n=60) were in the 26-35 age range, and 51.7% (n=75) were more than 35 years old. In this study the prevalence of lipodystrophy was 60.69%; 22.72% with lipohypertrophy, 51.14% with lipoatrophy, and 22.72% with mixed pattern.
The prevalence of lipodystrophy was 3.4% in the < 25 group, 47.7% in the 26-35 group, and 48.9% in the >35 group (p=0.039). Lipoatrophy prevalence was significantly higher in the 26-35 group (<25 = 2.2%, 26-35 = 57.8%, >35 = 40.0%; p= 0.040). Prevalence of lipohypertrophy was higher among those older than 35 years (<25 = nil, 26-35 = 30.0%, >35 = 70.0% ; p= 0.040). Among men, lipodystrophy prevalence seemed to increase with age (<25 = 6.1%, 26-35 = 27.3%, >35 = 66.7%; p= 0.248). Men younger than 25 years did not report lipoatrophy (26-35 = 50.0%, >35 = 50.0%; p= 0.004). Among women, prevalence of lipodystrophy (<25 = 1.8%, 26-35 = 60%, >35 = 38.2% ; p= 0.015) and lipoatrophy (<25 = 3.2%, 26-35 = 61.3%, >35 = 35.5% ; p= 0.046) was significantly higher in the 26- 35 group. Also, 79.5% of subjects reporting lipodystrophy were <40 (p=0.343). Prevalence of lipoatrophy (< 40=85.7%, >40 = 14.3%; p=0.001) and facial fat loss (< 40= 92.9%, >40= 7.1%; p=0.003) was significantly higher among men <40. Similarly, prevalence of lipoatrophy (< 40=87.4%, >40= 22.6%; p=0.095) and facial fat loss (< 40=80%, >40= 20%; p=0.078) was higher among women <40 years.

Conclusions: The prevalence of lipodystrophy did not seem to increase with aging among our study subjects. However, there was significantly higher prevalence of lipodystrophy and lipoatrophy including facial fat loss reported by younger subjects <40 years particularly between 26- 35 years.

Abstract: P_19

Pharmacology

Drug interaction in the elderly HIV-infected patient

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Background: Elderly HIV-infected patients may present particularities on both disease evolution and morbidity, as compared to younger patients. Moreover, elderly patients are more likely to take numerous medications due to their age-related condition. VISAGE is a French multidisciplinary study group focusing on elderly HIV-infected patients in order to evaluate and improve their therapeutic care. Our study "VISAGE 1" aimed to analyse potential drug interactions between antiretroviral drugs (ARV) and all other products taken by elderly HIV-infected patients. This 6-month prospective study involved patients treated for HIV infection and aging more than 60 years at the time of the study.

Material & methods: This 6-month prospective study has being performed from January to April 2009 in south east of France and has involved patients treated for HIV infection and aging more than 60 years at the time of the study. These patients were cared for in specialized hospital wards and in offices of physician members of HIV-dedicated city-hospital networks.
Patients were to fill an anonymous self-questionnaire for reporting their ARV, diseases other than HIV infection, and drugs or products regularly taken other than ARV. Analysis of drug interactions relied on the French drug agency (Afssaps) thesaurus by using the tool available on the website www.theriaque.org.

Results: 48 women and 188 men filled 236 questionnaires. Mean age was 66.7 years. Treatment of HIV infection was a classical combination of three ARV (2 nucleosides and 1 protease inhibitor or 1 non nucleoside) for 69.5% of patients. Among patients, 93.2% reported concomitant treatment with non-ARV drugs (4.9 +/- 3 drugs /patient) mainly prescribed for a cardiovascular mean. Most frequently used concomitant drugs were paracetamol (63.3% of patients), lysine acetyl salicylate (13%), bromazepam (9%) and rosuvastatin (9%). Clinically relevant drug interaction occurred in 45% of prescriptions, and the total number of drug interaction was 256, with more than 75% involving non-ARV drugs but were not in majority classified as serious. Associations were contra-indicated in 5 patients, and concerned 2 types of ARV / non-ARV association : ritonavir+alfusozine and protease inhibitor+simvastatin. Severity levels were “take into account” and “use with caution” for 50% and 33%, respectively.

Conclusion: Drug interactions were less frequent and less severe than expected in this population compared to literature on general population aged over 60 years. Drug interactions were mainly non-ARV treatments together. The two contra-indicated interactions had no clinical impact. Moreover, there were fewer ARV interactions than reported in the literature for this class of drug. Do the specialized physicians reduce their prescriptions given the numerous comorbidities existing with HIV infection, to reduced potential interactions? Or do older HIV-infected patients adopt a voluntary approach in order to reduce the number of treatments? A case-control study comparing the HIV population with non-HIV population was conducted to adress these questions (abstract VISAGE 2).

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