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Abstracts

Oral Presentations
Abstract: O_01

Neurology

PINCH in the cellular stress response to Tau-hyperphosphorylation

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Particularly interesting new cysteine-histidine-rich protein (PINCH) is an adaptor protein that our data have shown is required for neurite extension under stressful conditions in neurons. Our previous studies also report that PINCH is recalled by neurons showing decreased levels of synaptodendritic signaling proteins such as MAP2 or synaptophysin in the brains of human immunodeficiency virus (HIV) patients.

The current study addressed potential role(s) for PINCH in neurodegenerative diseases. Mass spectrometry predicted the interaction of PINCH with Tau and with members of the heat shock response. Our in vitro data confirmed that PINCH binds to hyperphosphorylated (hp) Tau and to E3 ubiquitin ligase, carboxy-terminus of heat shock-70 interacting protein, CHIP. Silencing PINCH prior to induction of hp-Tau resulted in more efficient clearance of accumulating hp-Tau, suggesting that PINCH may be stabilizing hp-Tau.

Accumulation of hp-Tau is implicated in more than 20 neuropathological diseases including Alzheimer’s disease (AD), frontotemporal dementia (FTD), and human immunodeficiency virus encephalitis (HIVE). Analyses of brain tissues from HIVE, AD and FTD patients showed that PINCH is increased, binds to hp-Tau and may accompany hp-Tau as it loses solubility during disease progression. These studies address a new mechanism by which AD and HIV may intersect.

No conflict of interest

Abstract: O_02

Neurology

Neurocognitive impairment and anxiety/depression in HIV-1 infected patients across Western Europe and Canada: CRANlum study age analysis

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Background: Life expectancy for patients infected with HIV has increased dramatically since the introduction of HAART. Patients infected at the age of 20 in North America and Europe are now estimated to have an average life expectancy of approximately 69 years. [1] Despite this, there is a scarcity of data regarding the effects of HIV-infection, antiretroviral therapy and comorbidities in the aging HIV-infected population.

Methods: CRANlum was a cross-sectional epidemiology study aiming to assess the prevalence of a positive screen for neurocognitive impairment (NCI) and depression/anxiety in HIV-1 infected patients > 18 y/o, comparing ARV-naïve and –experienced patients. The Hospital Anxiety and Depression Scale was used to screen for anxiety (HADS-A) and depression (HADS-D). The Brief Neurocognitive Screen (BNCS) was used to screen for NCI. A subgroup of patients also completed the MOS-HIV questionnaire to assess quality of life. Here we report results comparing data for patients < 50 and ≥ 50 years of age.

No conflict of interest
Abstracts

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Results: 2,834 evaluable patients [683 (24%) >50 y/o] from 15 countries were included. 61.5% of patients were male (<50 60.9%, >50 63.4%, p=0.24), 78.7% were Caucasian (<50 76.6%, >50 85.2%, p<0.0001) and 31.4% were HAART-naive (<50 35.9%, ≥50 17.3%, p<0.0001). Mean time from HIV diagnosis was 98.2 months (<50 87.2 months, ≥50 133.9 months, p<0.0001).

More patients in the older age group were married/in a civil partnership (<50 22.6%, >50 31.3%, p<0.0001), had children (<50 34.9%, >50 53.3%, p<0.0001), were unemployed (<50 27.5%, ≥50 50.8%, p<0.0001) and had a previous psychiatric diagnosis (<50 19.1%, ≥50 23.9%, p=0.0068). More patients in the younger age group had at least secondary school education (<50 84.1%, ≥50 75.3%, p<0.0001).

Overall, 15.7% of patients had a positive screen for depression (<50 15.3%, ≥50 17.0%, p=0.3039), 33.4% for anxiety (<50 34.1%, ≥50 31.4%, p=0.2087) and 41.4% for NCI (<50 42.1%, ≥50 38.1%, p=0.0608). From the MOS-HIV questionnaire, mean physical health summary scores were significantly higher in the younger group (52.67 vs 48.87, p<0.0001), but mental health summary scores were similar between age groups (49.27 vs 48.78, p=0.4024).

Conclusions: In this large epidemiologic study, the high prevalence of a positive screen for depression, anxiety and NCI did not differ between patients aged < or ≥ 50 years, regardless of significant differences in demographic constitution and disease characteristics between groups. These results support a strategy of regular screening for and clinical management of anxiety, depression and NCI for all HIV-infected patients.

Conflict of interest: The design, study conduct, and financial support of the clinical trial was provided by Abbott. Abbott participated in the interpretation of data, review, and approval of the poster. The presenting author is an Abbott employee and may hold stock or options.

Abstract: O_03

Neurology

Higher veterans aging cohort study (VACS) index scores are associated with concurrent risk of neurocognitive impairment

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Background: As HIV-infected (HIV+) individuals are living longer they are experiencing a broader range of non-AIDS diseases, and HIV infection has become a complex chronic disease with multiple interacting causes of morbidity. This has prompted the need for better ways to track the impact of comorbidities and multiple organ system dysfunction on the health of people living with HIV. The Veterans Aging Cohort Study (VACS) Index is a combined index of age, traditional HIV biomarkers (i.e. HIV-1 plasma RNA and current CD4 count) and non-HIV biomarkers (i.e. indicators of renal [eGFR] and liver [FIB-4] function, anemia [hemoglobin], and Hepatitis C co-infection). Higher VACS Index scores are predictive of mortality and some types of morbidity, but their relation with neurocognitive impairment (NCI) warrants investigation.

Materials and Methods: Participants included 1274 HIV+ individuals enrolled in various studies at the UCSD HIV Neurobehavioral Research Program (Ages 18-76 years; 85% male; 53% White; Median current CD4 count=370; 67% on ART; AIDS=64%, detectable plasma viral load among ART treated=44%). We computed the VACS Index on all participants. Neurocognitive function was assessed with an extensive battery assessing domains sensitive to HIV infection and consistent with Frascati criteria recommendations. Raw scores were converted to deficit scores using published, demographically-corrected normative standards.
Abstracts: O_04

Association of HIV-associated neurocognitive disorder with frailty in HIV-1-seropositive men

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Background. Frailty is significantly associated with several forms of cognitive impairment in HIV-uninfected adults. The association between frailty and HIV-associated neurocognitive disorders (HAND) is currently unknown. The primary objective of this study was to characterize the relationship of frailty and HAND in HIV-1-seropositive men while controlling for study site and patient characteristics.

Material and Methods. This was a retrospective cohort analysis of the Multicenter AIDS Cohort Study’s neurocognitive substudy enrolled from September 2005 to September 2011. Four US sites contributed data from 497 HIV-1-seropositive men who received a comprehensive neurocognitive battery, assessments of activities of daily living, and frailty phenotype testing. The primary outcome measure was a diagnosis of HAND (asymptomatic neurocognitive impairment, mild neurocognitive disorder, or HIV-associated dementia) or symptomatic HAND (mild neurocognitive disorder or HIV-associated dementia) defined as neurocognitive impairment from ≥2 of 8 cognitive domains with or without impairments in daily living, and frailty phenotype testing. The primary outcome measure was a diagnosis of HAND (asymptomatic neurocognitive impairment, mild neurocognitive disorder, or HIV-associated dementia) or symptomatic HAND (mild neurocognitive disorder or HIV-associated dementia) defined as neurocognitive impairment from ≥2 of 8 cognitive domains with or without impairments in daily living activities, respectively. Frailty was defined as a score within the lowest quintile on ≥3 of 5 assessments (grip strength, walking speed, involuntary weight loss, or self-reported exhaustion, and self-reported energy level). Multivariate logistic regression was used to evaluate the odds ratios of HAND or symptomatic HAND among those participants and were summarized in a global deficit score upon which NCI was defined.

Results: A logistic regression model on NCI showed a significant association with the VACS Index ($\chi^2=38.90$, $p<.001$). Another logistic regression model assessing the impact of all VACS Index components on NCI was significant ($p<.001$) and showed a significant effect of age ($\chi^2=6.01$, $p=.01$), hemoglobin ($\chi^2=6.77$, $p<.01$), and Hepatitis C co-infection ($\chi^2=5.59$, $p=.02$), whereas FIB-4 ($\chi^2=0.88$, $p=.35$), eGFR ($\chi^2=1.72$, $p=.19$), CD4 ($\chi^2=1.39$, $p=.24$), and plasma RNA ($\chi^2=2.75$, $p=.10$) were not significantly associated with NCI. A similar model including all VACS components along with AIDS revealed that AIDS ($\chi^2=13.88$, $p<.001$), hemoglobin ($\chi^2=5.57$, $p=.02$), and Hepatitis C co-infection ($\chi^2=6.90$, $p<.01$) were all significantly associated with NCI, while other VACS components were not. Subset analyses on participants with undetectable plasma viral load ($n=559$) showed a significant association between the VACS Index and NCI ($p<.001$). In this subset of participants, hemoglobin was the only significant predictor of NCI, even when AIDS was included in the model.

Conclusions: Higher VACS Index scores are associated with NCI. Among the VACS components, older age, lower hemoglobin and Hepatitis C co-infection were most strongly linked to HIV-associated NCI. Hemoglobin and Hepatitis-C continue to be associated with NCI in models including AIDS status. Among those with undetectable viral loads, hemoglobin showed the strongest association with NCI. These findings extend prior research on the potential usefulness of the VACS index in HIV infection and indicate that traditional indicators of HIV disease severity (i.e., AIDS diagnoses) and commonly encountered comorbidities (i.e., anemia and Hepatitis C co-infection) might each play unique roles in the clinical manifestation of neuroAIDS. Future research might examine the utility of the VACS in predicting incident NCI and its association with everyday functioning outcomes (e.g., HIV-related disability) and health-related quality of life.

No conflict of interest
with or without a diagnosis of frailty. Goodness of model fit was tested with the Hosmer-Lemeshow test.

**Results.** 191 (31.4%) men had normal cognitive performance and 303 (68.6%) had HAND. The prevalence of frailty was 8.6%. After adjustment for study site only, the odds ratio of HAND is 2.18 comparing those with vs. without frailty (for HAND: OR=2.18; 95% CI 1.05, 4.54; p=.036 and for symptomatic HAND: OR=2.99; CI 1.49, 5.96; p=.002). After adjustment for study site, age, race, education, employment status, CD4 lymphocyte count, smoking, marijuana use, drug use other than marijuana, intravenous drug use, and depression (by Beck Depression Inventory score >16), the odds ratio of HAND increased by 2.2 comparing those with vs. without frailty (for HAND: OR 2.2; 95% CI 1.03, 4.68; p=.042, and for symptomatic HAND: OR 2.8; 95% CI 1.37, 5.75; p=.005).

**Conclusions.** The increased odds of having HAND or symptomatic HAND among patients with frailty suggests a significant correlation between the two disorders. HAND is associated with poor medication management, lower employment rates, and an increased mortality rate; thus cognitive screening should be considered for all persons with frailty. Longitudinal analyses are needed to validate these cross-sectional results.

**Abstracts: O_05**

**HIV-1 envelope glycoprotein gp120 triggers a senescence phenotype in cultured human astrocytes**

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**Background:** Senescence is classically defined as an essentially irreversible proliferative growth arrest that is telomere-based, but it can also be induced by stress. In addition to the cell cycle arrest, senescent cells signal to the immune system through a secreted profile known as the senescence-associated secretory phenotype (SASP) to facilitate their own clearance producing pro-inflammatory cytokines and chemotactic factors. We previously demonstrated that 1) astrocytes undergo senescence in response to stress and 2) this response could be physiologically-relevant given that we are able to detect senescent astrocytes in aged and brain tissue and in neurodegenerative disease. HIV-1 infection of astrocytes or acute exposure to HIV-1 gp120 results in profound changes in astrocyte gene expression and the release of inflammatory mediators; however, the role of gp120 as an inducer of astrocyte senescence is still undefined.

**Materials & Methods:** In order to examine the cellular response to gp120, human astrocytes derived from fetal cortex were challenged with a range of concentrations of recombinant gp120 with different tropisms (IIIB and BaL). We investigated the effect of gp120 on the induction of the senescence phenotype through senescence-associated beta-galactosidase (SA β-gal) staining and by measuring the protein expression of senescence biomarkers p16INK4a and activated p38MAPK. We also profiled the secretion pattern of senescent astrocytes in vitro using an antibody array for pro-inflammatory factors and an interleukin-6 (IL-6) ELISA.
Results: We observed a significant increase in SA β-gal activity in astrocytes treated with gp120 Bal or gp120 IIIB (p< 0.05, for all concentrations tested vs. vehicle-treated control astrocytes, Student’s t-test). Furthermore, gp120 treatment (Bal and IIIB) increased the expression of p16INK4a and the phosphorylation of p38MAPK. We found that senescent astrocytes produce a number of inflammatory cytokines including interleukin-6 (IL-6) (p<0.01, Student’s t-test vs. pre-senescent) indicative of a SASP, which seems to be regulated by p38MAPK.

Conclusions: While it seems likely that HIV-1 viral products are inducing the senescence phenotype in astrocytes in vitro, further studies will be required to determine the physiological significance of this finding. Astrocyte senescence may be an important component of the development and progression of HAND through the generation of a SASP and/or the perturbation of astrocyte functions that are critical for the maintenance of neuronal homeostasis.

Abstract: O_06

Immunology

Biological aging in HIV-infected individuals in South Africa: a case-control study

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Background: Cellular senescence is likely to be a key factor contributing towards premature biological aging in HIV-infected individuals. In sub-Saharan Africa, there are few data relating to biological aging in HIV infection. We assessed two candidate biomarkers of aging (BoA), telomere length and CDKN2A expression (a mediator of cell senescence), in South African HIV-infected adults and healthy HIV-seronegative individuals.

Methods: Case-control study of 486 adults aged ≥ 30 years, composed of 236 HIV-infected adults and 250 age- and gender-matched HIV-seronegative individuals. Biological aging was evaluated by measurement of telomere length and CDKN2A expression in peripheral blood leukocytes.

Results: The mean ages of the HIV-infected and HIV-seronegative groups were 41.0±0.5 years and 42.6±0.6 years, respectively. HIV-infected individuals had lower body mass index and were less likely to smoke or consume alcohol (all p<0.05). Of the HIV-infected adults, 87.1% were receiving anti-retroviral therapy (ART), their median CD4 count was 468 cells/μL and 84.3% had undetectable viral load. Telomere length was significantly shorter in HIV-infected individuals compared to HIV-seronegative individuals (mean relative T/S ratio [Rel T/S]±SE: 0.91±0.007 vs. 1.07±0.008, p<0.0001). CD2NKA expression was higher in HIV-infected participants compared to HIV-seronegative individuals (mean expression 0.45±0.02 vs. 0.36±0.03, p=0.003). Lower current CD4 counts were associated with shorter telomere length and greater CDKN2A expression in participants on ART with non-detectable viral load (p-trend=0.02 telomeres; p-trend=0.04 CDKN2A).

Conclusions: Both biomarkers indicated increased biological aging in the HIV-infected individuals compared to HIV-seronegative individuals. These findings have potentially important implications for age-related morbidity among the millions of patients receiving ART in Africa.

No conflict of interest
Abstract: O_07

Active Hepatitis C virus (HCV) infection, HIV+ status and low income are associated with shorter leukocyte telomere length in a cohort of HIV+ and HIV- adults.

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Background: Telomeres contain DNA repeats and protect the ends of chromosomes. Telomeres shorten with age, thus telomere length (TL) is considered a marker of aging. Oxidative stress related to HIV-induced inflammation, chronic immune activation, antiretroviral therapy (ART) and/or ART-mediated inhibition of telomerase activity could lead to accelerated telomere shortening. We investigated leukocyte TL (LTL) in HIV+ and HIV- adults, and examined factors associated with shorter LTL.

Material & Methods: In this prospective study, blood was collected from HIV+ and HIV- adults (>19 years) enrolled in the CARMA cohort study on HIV therapy and aging. LTL was measured using qPCR. Univariate linear regression models were used to examine relationships of potential explanatory variables with LTL. In addition to HIV status, univariately important variables (p<0.15) were used as candidates in the development of a multivariate model. Linear regressions were used to investigate HIV-related factors among HIV+ individuals.

Results: LTL data was obtained for 229 HIV+ subjects (median [IQR] (range) = 40 [33-49] (20-77) years, 79% female) and 166 HIV- controls (38 [31-49] (21-73) years, 71% female). Shorter LTL were univariately associated with older age, pack-years smoking, illicit drug use, and active HCV infection (all p<0.0001), HIV+ status (p=0.031), and income <$15,000/year (p=0.0002). Having an older father (p=0.0001), an older mother (p=0.021) and being Black (p=0.031) or South Asian (p=0.018) vs. White were univariately associated with longer LTL. Several variables showed significant interactions with HIV status, notably smoking, illicit drug use, and low income; whereby these were associated with shorter LTL among HIV- subjects only. In addition, a number of variables had a high level of correlation, including: illicit drug use/ethnicity/HCV and income/smoking, increasing modeling complexity. In the final multivariate model (R²=0.24) that included a significant HIV*income interaction variable (p=0.034), older age (p<0.0001), HIV+ status (p=0.004), income <$15,000/ year (p=0.001) and active (p=0.004) but not cleared HCV infection (p=0.22) vs. HCV- were associated with shorter LTL. Father's age at birth, although important, was not included in the model as data was missing for more than half (210/395) of subjects. Among HIV+ subjects, neither ART duration, CD4 count, CD4 nadir, time since HIV diagnosis, number of ART interruptions nor having detectable HIV viremia were univariately associated with LTL. The same was true among the HIV+ subgroup with undetectable viral loads (n=126).

Conclusions: These results suggest that beyond advancing age, HIV+ status, active HCV infection and low income are the strongest predictors of LTL and may therefore affect telomere maintenance and cellular aging. Low income may act as a surrogate for a number of lifestyle and environmental factors. It is noteworthy that some factors shown to be associated with shorter LTL (e.g. smoking) emerged among HIV- controls but were less important in the HIV+ group, suggesting other factors may overwhelm their effect in HIV+ individuals. Active HCV’s association with shorter LTL may indicate that ongoing HCV-related chronic immune activation and/or inflammation affect LTL. We saw no evidence that ART-related factors impact LTL. Further study should examine the potential impact of HCV therapy on LTL.
Abstract: O_08

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

Tenofovir accelerates bone mass loss of the lumbar spine in the first years of menopause in HIV infected women

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Background: Previous studies have shown that HIV-infected postmenopausal women have higher rates of bone loss than HIV negative women. No studies so far have analyzed the slope of bone loss across the menopausal transition period. We hypothesized that in HIV infected women BMD decreases in the postmenopausal period and Tenofovir (TDF) exposure may contribute to this impairment. The aim of the study was to identify predictors of BMD in HIV infected women entering menopause and to evaluate the pre- and postmenopausal BMD change.

Methods: Women with at least one DEXA measurement both in the pre- and postmenopausal periods were enrolled. The observation period was divided into four time windows: 'Reproductive Period', 'Menopause Transition Period', 'Early Menopause Period', 'Late Menopause Period'. BMD of the lumbar spine (L1-4) and femur neck were measured by DEXA. Lowess smoothing curves were drawn to analyze impact of menopause and TDF on BMD. Three different longitudinal linear regression models with random effects were built. Longitudinal regression analysis fits cross sectional time series regression models and allows to analyze repeated measures for each patient.

Results: Fifty-five women were included. Median age at enrollment was 46 years (IQ range 44-49). Median observation period was 16 months (IQ range 8; 23) and 33 months (IQ range 23; 72) pre-menopause and postmenopausal, respectively. At enrollment mean CD4 cell count was 553 cell/mL (±269.62) and HIV-VL was undetectable in 77.5% of patients: 6 women were not undergoing ART and the most commonly used associations were 2NRTI+NNRTI (40.8%) and 2NRTI+PI/r (30.6%). Most common backbone TDF/FTC(46.9%) and ABC/3TC (20.4%). At the time of inclusion in the cohort osteopenia and osteoporosis were present in 60% and 3.64%, respectively. At the time of last DEXA evaluation osteopenia and osteoporosis were present in 78.18% and 36.36%, respectively. The impact of menopause on lumbar BMD was depicted using a lowess smoothing analysis according to current TDF exposure (as treated model). Lumbar BMD change predictors were years from menopause and TDF current exposure in the 'Early Menopause Period' and years from menopause, Baseline lumbar BMD, BMI and vitD supplementation in the 'Late Menopause Period'.

Discussion: This is the first study analysing BMD across menopause. BMD was stable in the pre-menopause period while BMD loss characterized the post-menopause period. Traditional risk factors contributed to BMD change in the post -menopause period. Current TDF exposure was independently associated with BMD change in the 'Early Menopause Period' only, but not confirmed in the 'Late Menopause Period', suggesting a compensating mechanism occurring after the second year postmenopause.

No conflict of interest
Abstract: O_09

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

Lean and fat mass are stronger predictors of impaired functional status than bone

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Background: Low lean mass (LM), low bone mineral density (BMD), and increased body fat are associated with disability and frailty among elderly persons. The goal of the present study was to assess the relationship between body composition components and functional status among middle-aged persons with HIV-1 infection.

Material & Methods: We performed a prospective 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. Low functioning (LF) and high functioning (HF) subjects were identified by clinical criteria and matched by age, gender, and time since HIV diagnosis. Body composition was measured by dual-energy X-ray absorptiometry. Between group comparisons utilized mixed effects (reported as mean ± SE) or conditional logistic regression. Conditional logistic regression was utilized for primary case-control analysis with best model chosen using Akaike information criterion. BMD (total hip and lumbar spine), LM (total body LM and appendicular skeletal muscle index [ASMI]), and fat (percent body fat, fat normalized to height, and trunk to limb fat ratio) were each included in conditional logistic regression. The resulting three predictors were considered for the final model, which included covariates significant at p<0.05.

Results: 30 LF were identified and matched to 48 HF subjects; mean age was 52.8 ± 0.5 years, CD4 T-cell was 598 ± 30.9, 96% HIV-1 viral load <48 copies/mL. 21% were female, 77% white, and 17% Hispanic. LF and HF were similar in age (53.0 ± 0.8, 52.9 ± 0.6 years), duration of ART (145 ± 15.2, 146 ± 12.0 months), tenofovir use (OR: 1.43; 0.40, 5.08), and CD4 T-cells (535 ± 44.4, 655 ± 37.0 cells/µL; all p>0.2). LF subjects had significantly lower hip BMD (0.812 ± 0.023 vs. 0.91 ± 0.0192 g/cm², p=0.001) and spine BMD (0.917 ± 0.026 vs 1.007 ± 0.021 g/cm², p=0.01). LF trended towards a higher body fat percentage (28.1 ± 1.6% vs 24.7 ± 1.4%, p=0.07), but fat normalized to height and ratio of trunk to limb fat ratio were not significantly different (1.930 ± 0.183, 2.102 ± 0.153, p>0.3). LF subjects had lower LM (46.8 ± 1.7 kg vs 51.5 ± 1.4 kg, p=0.01) and lower ASMI (6.8 ± 0.2 vs 7.7 ± 0.2, p=0.002).

In conditional logistic regression, total hip BMD, ASMI, and percent body fat were selected as the best variables in each category by AIC. In the final model, BMD was no longer significant (0.01 unit OR: 0.95, 95% CI 0.88, 1.02; p=0.16). Lower ASMI (OR 2.6, 95% CI 1.4, 4.8) and higher percent fat (OR 1.1; 95% CI 1.0, 1.24) remained significant predictors of low functional status (p=0.003, p=0.01, respectively). Results were robust to inclusion of age and CD4 count.

Conclusions: Although BMD was significantly different between LF and HF groups, low muscularity and higher adiposity were better predictors of functional status among middle-aged HIV-1 infected persons. Further studies should investigate the benefit of maintained or increased muscle mass and avoidance of excess body fat on the functional independence of persons aging with HIV-1 infection.

This data was presented in part at the Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, March 2013

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Abstract: O_10

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

The effect of HIV and inflammation on lung function decline

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Introduction/Background: Increasing evidence suggests an association between HIV and obstructive lung disease (OLD), perhaps through inflammatory pathways. In prior cross-sectional analysis, we showed that higher plasma HIV viral load was associated with increased risk for OLD. However, longitudinal data characterizing lung function decline remains sparse. We hypothesized that both HIV disease and inflammatory markers would be associated with more rapid lung function decline.

Materials & Methods: Semi-annual clinical, laboratory, and spirometric data were collected in the AIDS Linked to the IntraVenous Experience (ALIVE) study, an observational cohort of HIV+ and HIV– injection drug users in Baltimore, Maryland. Repeated measure random-effects models estimated the independent effects of HIV infection, RNA levels, and CD4 cell count on annual decline in forced expiratory volume in one second (FEV1) after adjusting for baseline demographics and time-varying smoking status. Using a standard formula, FEV1 data were translated into estimated lung age to represent the average age of healthy individual with similar spirometric function.

Results: Among 1064 participants, we performed 4555 spirometry measurements during a median of 2.75 years (range 0.5 to 3.9) of observation. At baseline the cohort was 49 ± 7 years old, 65% male, 91% African American, 30% HIV+ and >94% were current or former smokers. The prevalence of OLD was 16% and did not differ by HIV status (p = 0.74). After adjustment for age, sex, race, body mass index, and smoking pattern, HIV-infection was associated with a 174 mL lower absolute FEV1 (p <0.01). The annual rate of FEV1 decline among HIV negative persons (−24.2 mL/year) did not differ significantly between HIV+ persons with undetectable HIV RNA (−35.7 mL/year) or RNA of 400 to 75,000 copies/mL (−28.3 mL/year). However, HIV+ persons with HIV RNA >75,000 copies/mL had significantly greater annual FEV1 decline (−107 mL/year; p = 0.003); these associations persisted after adjusting for ART use. Similarly, persons with CD4 cell counts from 100 to 200 and <100 cells/mm³ were associated with more rapid FEV1 decline (−61.4 and −65.6 mL/year; p = 0.025 and 0.017, respectively). In separate adjusted models incorporating inflammatory biomarkers measured near baseline, IL-6 was independently associated with lower FEV1 (-35.5 mL per log increase in IL-6 level, P=0.042); no association was seen with CRP. Despite similar biological age at baseline, the difference in estimated lung age was 3.9 years older among HIV-infected compared to uninfected persons, after adjusting for smoking (P=0.001).

Conclusions: Markers of advanced and uncontrolled HIV disease were associated with more rapid decline in lung function. The decline seen with high viral load is greater than the 50 to 70 mL/year decline seen in smokers. The effect of HIV on lung age was roughly equivalent to smoking an additional 25 pack-years. These findings expand the current state of knowledge regarding the association between HIV infection and chronic lung disease and suggest that optimal ART with HIV virological suppression may diminish the accelerated decline in lung function.

No conflict of interest
Abstract: O_11

Geriatrics and clinical care

Effect of aerobic exercise training in older HIV-infected patients

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Introduction/Background: HIV-infected patients have increased risk of age-related conditions, including cardiovascular disease, osteoporosis, and frailty. In adults without HIV, these age-related conditions are strongly associated with poor exercise capacity, but improve with exercise training, decreasing morbidity and disability. We hypothesized that aerobic exercise training (AEX) in older HIV-infected patients would increase exercise endurance (time on treadmill), but high-intensity training would be required to increase aerobic capacity (oxygen utilization at peak exercise, peakVO2).

Material & Methods: Eligible subjects included older (50+ years) sedentary HIV-infected men receiving antiretroviral therapy and without an AIDS defining illness (ADI) in the previous 6 months. Twenty-two subjects were randomized to high-intensity (n=12) or low-intensity (n=10) AEX. Both groups trained 3x/week for 16-weeks in a research gym under supervision of an exercise physiologist, who encouraged maintenance of calorie intake and outside activity. High-intensity aerobic training (Hi-AEX) consisted of treadmill training for 4-weeks with exercise target of 30 minutes at 40-60% heart rate reserve (HRR) followed by 12-weeks with exercise target of 60 minutes at 75-80% HRR. Low-intensity aerobic training (Lo-AEX) consisted of one mile of self-paced walking on an indoor track followed by stretching. Paired Student's t-tests were used to compare baseline and 16-week results.

Results: Participants had a median age of 56 years (range 52-69) and 91% were African American. Although HIV was well controlled (median CD4 476 cells/mm³; 94% HIV-1 viral load <50 c/mL), 44% of participants had a history of prior ADI. Six participants did not complete the study due to medical disqualification (n=3, stroke, lung cancer, gastric ulcer), lost-to follow-up (2), or withdrawal (1), a 27% attrition rate. PeakVO2 increased 17% in the Hi-AEX group (n=9) (mean ±SE pre. vs. post: 1.89 L/min ± 0.19 vs. 2.12 ± 0.15, p=0.03), but did not change in the Lo-AEX group (n=7) (1.73 L/min ± 0.17 vs. 1.75 ± 0.13, p=0.9). Time on treadmill increased 25% in the Hi-AEX group (11.7 mins ± 0.8 vs.14.3 ±0.6 p=0.02) and 11% in the Lo-AEX group (11.0 mins ± 0.5 vs.12.1 ±0.5 p=0.04). Both groups had clinically significant improvement in ambulatory function measured by the 6-minute walk distance (Hi-AEX, Δ62 m ±18, p=0.01; Lo-AEX, Δ54 m ±14, p<0.01). There was no significant change with training in fasting blood tests (lipids, glucose, insulin), weight, waist circumference, percent body fat or total lean muscle mass (DEXA) (all p>0.4). Between group differences were not statistically significant.

Conclusions: This study presents novel results in older HIV-infected men that demonstrate the safety, feasibility, and efficacy of AEX training to increase aerobic capacity, endurance, and ambulatory function in this complex patient population. The benefits of AEX combined with weight loss and resistance training to improve lipodystrophy syndrome, sarcopenia, and osteoporosis warrant further investigation. Future research is needed to identify the mechanisms for increased aerobic capacity, and apply the findings to design of an exercise effectiveness trial.

No conflict of interest
Abstract: O_12

Geriatrics and clinical care

Comorbidities and AIDS predict the frailty phenotype in men with treated HIV-1 infection

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Background: Adults aging with HIV infection due to effective treatment are at risk for age-related comorbidities and syndromes, including frailty. The objective of this study was to estimate the prevalence of the frailty phenotype (FP), by age, among HIV-infected (HIV+) and –uninfected (HIV-) men with similar lifestyles, and to examine predictors of fluctuation in expression of the FP.

Methods: The MACS is a prospective, observational, cohort study of HIV+ and HIV– men who have sex with men. Participants were included in our study if they completed ≥1 study visit between October 1, 2007 and September 30, 2011. The frailty phenotype (FP) was assessed as defined by Fried and colleagues, requiring ≥3 of 5 criteria: slowness, low energy, unintentional weight loss, weakness, and low physical activity. FP conversion was defined as expression of the FP at the second, but not the first, visit in a pair of consecutive person-visits (FP- to FP+); reversion was defined as FP+ to FP-. Predictors were measured at the first visit of each person-visit pair. Univariate (OR) and multivariate (aOR) odds ratios and 95% confidence intervals ([,]) were estimated using logistic regression models with generalized estimating equations to account for within-person correlations from the repeated measurements.

Results: 2,052 MACS participants (992 HIV+, 1,060 HIV-) contributed 11,134 person-visits (5,366 HIV+, 5,768 HIV-); the number of completed study visits was similar by HIV status (median=6 [25%, 75%=4, 7] person-visits in both groups, p=0.76). 25% (503/2,052) of men were FP+ at ≥1 study visit. The proportion of FP+ person-visits increased with increasing age regardless of HIV status, but was greater in HIV+ men for all age groups and significantly so for ages 50-64: <40yo: 6% vs. 4%, p=0.15; 40-44yo: 7% vs. 5%, p=0.23; 45-49yo: 9% vs. 9%, p=0.91; 50-54yo: 15% vs. 6%, p<0.01; 55-59yo: 14% vs. 8%, p=0.01; 60-64yo: 17% vs. 10%, p=0.03; ≥65yo: 35% vs. 17% p=0.14. Of those who were ever FP+, 46% (n=230) were FP+ at only one visit, demonstrating fluctuation in FP status. In multivariate models, the odds of FP conversion were increased among HIV+ men with a history of AIDS (aOR=2.23 [1.49, 3.34]), but not among HIV+ men without AIDS (aOR=1.25 [0.97, 1.60]), compared to HIV- men. Depressive symptoms, diabetes, kidney disease, use of PI-based HAART, and use of a non-HAART antiretroviral therapy were also associated with significantly higher aOR of FP conversion. The odds of FP reversion were increased among younger men and those reporting injection drug use, and decreased among those with kidney disease. Among HIV+ men, FP reversion was more likely in non-Hispanic Black men and less likely in men with kidney disease.

Conclusions: Although HIV+ men had a greater prevalence of the FP in all age groups, age-related comorbidities and AIDS predicted conversion from FP- to FP+, suggesting that comorbidities may account for the increase in odds of FP expression among HIV+ compared to HIV- men.

No conflict of interest
Abstract: O_13

Frailty and circulating concentrations of proinflammatory cytokines and chemokines in HIV-infected and –uninfected men in the Multicenter AIDS Cohort Study (MACS)

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Background: Frailty is an aging-related condition that is a prognostic indicator of negative health outcomes in HIV-uninfected elderly populations. In the MACS, HIV-infected men aged 50-64 have a higher prevalence of frailty than similarly aged HIV-uninfected men, and presence of a frailty-related phenotype predicted decreased AIDS-free survival after starting antiretroviral therapy (ART). In the general population, frailty is associated with elevated serological markers of inflammation, particularly IL-6, but the relationship between frailty and treated HIV infection has not been determined.

Material & Methods: The frailty phenotype (FP) was assessed at 8 semiannual MACS study visits according to the definition of Fried et al: presence of ≥3 of the following 5 criteria: unintentional weight loss, low hand grip strength, exhaustion, slow walking speed, and low physical activity. For this study, frailty was defined as expression of the FP (FP+) at two consecutive study visits, and non-frailty as being FP- at two consecutive visits. Serum concentrations of cytokines and chemokines within one year of frailty assessment were available for 602 men (117 HIV-/FP-, 20 HIV-/FP+, 393 HIV+/FP-, and 72 HIV+/FP+) who were studied in a larger sampling of ~12,500 stored specimens from 1141 MACS participants. The vast majority of HIV+ men were receiving ART and had undetectable HIV viral loads. Data were analyzed by generalized gamma regression with adjustment for age, ethnicity, study center, education, BMI, smoking, hepatitis C infection, depression (CES-D >16), high blood pressure, diabetes, dyslipidemia, kidney disease, liver disease, and cancer.

Results: Among HIV+ men, those with the FP had significantly higher concentrations of the cytokines IL-6, and TNF-α; the chemokines IL-8, IP-10, MCP-4, and TARC; and C-reactive protein (differences of 10-45% relative to the HIV- men). For most of these markers, the differences between FP+ and FP- HIV- men were of similar magnitude, but were not significantly different, likely due to a smaller sample size. However, concentrations of C-reactive protein (CRP) were similar between HIV- FP+ and FP-.

Conclusions: Several inflammatory markers had significant associations with FP in HIV+ men. Elevated IL-6, TNF-α, and CRP are consistent with previous reports and suggest monocyte activation. Elevation of IP-10, which is produced in response to interferons, is consistent with T-cell activation. Although these cross-sectional data cannot establish causation, they support the notion that inflammatory pathways may contribute to onset of the frailty phenotype in HIV+ men.
Abstract: O_14

Metabolic/ cardiovascular complications

A cross-sectional analysis of biological CVD risk factors among HIV clients in a resource-limited setting: Findings from a CVD/HIV integration pilot

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Background: As HIV care and treatment programs are scaled up and access to ART continues to expand in resource-limited settings, people living with HIV are living longer, and therefore at an increased risk for developing CVD. Additionally, HIV infection itself and antiretrovirals increase one’s risk for CVD. Given this interplay between CVD and HIV, FHI 360 launched a pilot program integrating CVD screening into existing HIV services in Kenya.

Material & Methods: Cross-sectional data on client demographics and biomedical risk factors were collected in the five pilot sites among clients accessing HIV counseling and testing and HIV care and treatment services from September 2009 to September 2010. Statistical analysis was carried out utilizing SPSS version 17.0. Descriptive analysis was conducted using simple frequencies. Correlation analysis using the spearman rho was run to examine associations between HIV status and CVD risk factors. Logistic regression analysis was carried out to measure the association of CVD risk factors between (i) HIV-negative and HIV-positive clients, (ii) HIV-negative and ART clients, and (iii) HIV care clients (HIV positive clients in care but not on ART) and ART clients.

Results: A total of 4,095 clients were screened during the 12-month pilot period. ART clients were more likely to have elevated blood pressure (OR 1.364, p=0.005) compared to HIV-negative clients. There was no significant difference in BMI between HIV-negative and ART clients. However, ART clients were 1.754 times as likely (p<0.001) to be hypertensive, 1.320 times as likely to have high BMI (p=0.020), and twice as likely (OR 1.961, p<0.001) to have a high waist circumference compared to HIV Care clients. Clients on ART for less than one year were less likely to have high blood pressure (13%, n=12) and high total cholesterol levels (10%, n=4) compared to those who had been on ART for one to three years (26% and 32%, respectively) and four years or longer (24% and 28%, respectively). HIV-positive clients on ART for one to three years had the highest prevalence of high BMI (26%, n=51).

Conclusions: This cross-sectional study demonstrates an association between biological CVD risk factors and ART. Among this study population, the highest frequency of biological CVD risk factors (elevated blood pressure, high BMI, and high waist circumference) was found among ART clients. This analysis also demonstrated an association between CVD risk factors and the client’s duration on ART. Given the associated risk between elevated blood pressure, high waist circumference, and high total cholesterol with CVD, it is recommended that screening for CVD risk factors be part of the standard of HIV care for clients receiving ART. This analysis also highlights the need for a prospective cohort study, which would allow HIV clients to be followed over time and generate causal relationships between HIV infection, ART use, and risk for CVD. Such a study is critical given the increasing rates of CVD and existing high prevalence of HIV in resource-limited countries such as Kenya.

No conflict of interest
Abstract: O_15

Metabolic/ cardiovascular complications

Accelerated cardiovascular ageing in treated HIV males: impact of the Framingham Risk Score on the difference between chronologic and vascular age

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Background: The prediction of cardiovascular disease (CVD) risk in treated HIV patients (pts) remains poorly understood. The Framingham Risk Score (FRS) calculator, recently updated (D’Agostino, Circulation 2008), is recommended for CVD risk assessment in HIV pts. The difference between chronologic age and vascular age, (D’Agostino, 2008), defined as the age of a person with the same predicted risk and normal levels of risk factors, is a measure of risk factor burden and may be considered a surrogate for accelerated cardiovascular aging. We calculated the difference between both the 2001 and the updated FRS and chronologic age in a cohort of treated HIV males.

Methods: We retrospectively analyzed data obtained at the baseline visit on stable, treated HIV males assessed between 2005 - 2010 at an HIV metabolic clinic. The FRS was calculated using both the 2001 NCEP Guidelines (FRS-old) and the updated 2008 Calculator (FRS-new). We stratified patients into 4 age groups: 20-39, 40-49, 50-59, and 60-75 years. Results are reported as mean ± SD and median (95% CI). Chronologic age and vascular age, calculated using the FRS-old and FRS-new, were compared by ANOVA and T-test or comparison of 95% CI both within and between age groups.

Results: The FRS was determined in 1435 predominantly Caucasian males stratified by age into those 20-39 (n=214), 40-49 (n=878), 50-59 (n=274) and 60-75 (n=69) years old. The cohort’s baseline characteristics included: median duration of HIV infection - 173 m (range 3-308); median age - 46 (range 20-75); mean CD4+ T-cells of 560 ± 260; and 60 % with undetectable HIV-RNA. The median chronologic, FRS-old vascular age, and FRS-new vascular age within the age groups were: (20-39) - 37, 34 and 40; (40-49) - 44, 48 and 54; (50-59) - 53, 64 and 64; (60-75) - 63, 76 and 80. Differences in median chronic age between age groups and in both the median FRS-old and FRS-new vascular ages between age groups were highly significant. Both the FRS-old and FRS-new vascular ages were significantly greater than the chronologic age within all groups (p=0.0001). The FRS-new vascular age was greater than the FRS-old vascular age in the 20-39 and 40-49 year old groups (p=0.0001) but not in the 50-59 and 60-75 year groups (p=NS). The difference between the median FRS-old vascular age and chronologic age across age groups was -3, +4, +11, and +13 years respectively, and between the FRS-new vascular age and chronologic age across age groups was +3, +10, +11, +17 years respectively.

Conclusions: We found a significant age group dependent increase in vascular age ranging between 3-17 years more than chronologic age in treated HIV pts older than 20 years using the updated FRS calculator. Vascular age determined using the updated FRS calculator was consistently greater than that obtained with the 2001 FRS calculator in pts younger than 50. Differences between vascular and chronic age represent an increased CVD risk in all age groups of these HIV pts. This suggests that accelerated cardiac ageing is common and must be aggressively evaluated.

No conflict of interest
Abstract: O_16

Geriatrics and clinical care

Similar outcomes in older versus younger patients over 96 weeks in treatment-naïve, HIV-1-infected patients treated with Rilpivirine or Efavirenz

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Background: As life expectancy of HIV-1–infected patients increases, there is interest in how overall trial results apply to the older patient considering that hepatic, renal and immune function decline with age, and comorbidities increase. We evaluated potential outcome differences in older versus younger patients in the Phase III ECHO and THRIVE trials at Week 96.

Materials & Methods: HIV-infected treatment-naïve adult patients were randomized to receive rilpivirine (RPV) 25mg qd or efavirenz (EFV) 600mg qd (1:1), plus either tenofovir disoproxil fumarate (TDF)/emtricitabine (ECHO) or TDF/emtricitabine, lamivudine/zidovudine or abacavir/lamivudine (THRIVE). Efficacy and safety outcomes were assessed over 96 weeks within age strata post hoc.

Results: 1368 patients were treated (<50 years [younger], n=1242; ≥50 years [older], n=126). Mean baseline HIV-1 RNA was 5.0 log₁₀ copies/mL and median CD4+ cell count was 256 cells/mm³. At Week 96, virologic responses (HIV-1 RNA <50 copies/mL; FDA snapshot analysis) for RPV were 76% (471/617) and 77% (53/69) in younger and older patients, respectively, and for EFV, 76% (474/625) and 84% (48/57), respectively. Median changes in CD4+ (cells/mm³) from baseline for RPV were 263 and 237 in younger and older patients, respectively, and for EFV, 251 and 278, respectively. Rates of discontinuations due to adverse events (AEs) for RPV were 3.9% and 5.8% in younger and older patients, respectively, and for EFV, 8.5% and 10.5%, respectively. Rates of at least possibly related Grade ≥2 AEs for RPV were 17% and 13% in younger and older patients, respectively, and for EFV, 33% and 39%, respectively. The rates of Grade ≥2 nervous system disorders at least possibly related to study drug showed no trend for being worse in older versus younger patients for either RPV or EFV. Rates of Grade ≥2 psychiatric disorders at least possibly related to study drug for RPV were 6.3% and 2.9% in younger and older patients, respectively, and for EFV, 9.1% and 14.0%, respectively. Further, the rates of Grade ≥2 skin and subcutaneous tissue disorders at least possibly related to study drug for RPV were 1.6% and 1.4% in younger and older patients, respectively, and for EFV, 8.2% and 15.8%, respectively. Changes in total cholesterol and LDL-cholesterol were minimal for RPV in both age groups, while increases in both lipid parameters were observed for EFV in older and younger patients. HDL and triglyceride changes were small and showed no trend for worsening by age. Median changes from baseline in creatinine, aspartate aminotransferase and alanine aminotransferase were small and similar between treatment groups and age categories.

Conclusions: RPV-treated patients showed similar virologic and immunologic responses across age groups; in EFV-treated patients, efficacy outcomes were higher in older patients. In contrast to expectations, RPV- and EFV-treated older patients generally did not experience more neurological, Grade ≥2 drug-related AEs or hepatic and renal Grade ≥3 lab abnormality reporting frequencies versus younger patients. Grade ≥2 related psychiatric and skin event rates increased in older EFV patients. Incidences of Grade ≥2 drug-related AEs were generally lower with RPV versus EFV, regardless of age.

Conflict of interest: David Anderson, Yaswant Dayaram, and Deborah Schaible are employees and shareholders (excluding diversified mutual funds) of Janssen Services, LLC. Bruce Coate is an independent contractor for Janssen Research & Development. Robert Ryan is an employee and shareholder (excluding diversified mutual funds) of Janssen Research & Development.
Abstract: O_17

Pharmacology

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF demonstrates comparable efficacy and favorable tolerability to Efavirenz/Emtricitabine/Tenofovir DF and to Ritonavir-boosted Atazanavir plus Emtricitabine/Tenofovir DF in patients ≥50 years


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Background:
Elvitegravir/cobicistat/emtricitabine/tenofovir DF which was formally known as QUAD [STB] demonstrated non-inferior efficacy to EFV/FTC/TDF [ATR] (88% vs. 84%) and ritonavir-boosted atazanavir (ATV+RTV) plus emtricitabine/tenofovir DF [FTC/TDF], (90% vs. 87%) at Week 48, with favorable tolerability. Efficacy and safety of ARVs in patients ≥ 50 yrs is important given the aging HIV population.

Material & Methods: An analysis of safety and efficacy (% with HIV-RNA <50 copies/mL at Week 48 per FDA snapshot analysis) in two Phase 3 STB studies in patients ≥ and < 50 yrs was performed.

Results: Subjects in the 236-0102 study by age were ≥ 50 yrs (n=49) and < 50 yrs (n=299) for STB vs 56 and 296 for ATR. Rates of virologic suppression (HIV-1 RNA < 50 c/mL) were comparable between age subgroups, STB (86 vs 88%) and ATR (82 vs 84%). CD4 changes, adverse events and changes in eGFR are given in Table 1 below.

In Study 236-0103, 48 subjects were ≥ 50 yrs and 305 were < 50 yrs for STB, vs 48 and 307 for ATV+RTV +FTC/TDF. Rates of virologic suppression were comparable between age subgroups, STB (94 vs 89%) and ATV+RTV+FTC/TDF (88 vs 87%). CD4 changes, adverse events and changes in eGFR are given in Table 1 below.

Conclusions: STB efficacy was comparable to ATR and ATV+RTV+FTC/TDF, in younger and older subjects, with fewer neuropsychiatric or rash AEs than ATR and with a similar tolerability profile to ATV+RTV+FTC/TDF in patient ≥ 50 yrs.

Table 1: Age Analysis

<table>
<thead>
<tr>
<th>GS 236-0102: STB vs Atripla</th>
<th>STB ≥50 yrs (n=49)</th>
<th>STB &lt;50 yrs (n=299)</th>
<th>ATR ≥50 yrs (n=56)</th>
<th>ATR &lt;50 yrs (n=296)</th>
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<tr>
<td>Efficacy</td>
<td>86%</td>
<td>88%</td>
<td>82%</td>
<td>84%</td>
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<tr>
<td>Mean CD4 increases cells/mm³</td>
<td>199</td>
<td>246</td>
<td>194</td>
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<td>AEs</td>
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<tr>
<td>-AEs Leading to DC</td>
<td>6.1%</td>
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<td>-Serious AEs</td>
<td>18.4%</td>
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<td>-Neuropsych</td>
<td>32.7%</td>
<td>44.5%</td>
<td>60.7%</td>
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<tr>
<td>-Rash</td>
<td>10.2%</td>
<td>18.1%</td>
<td>28.6%</td>
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<td>Median changes in eGFR mL/min</td>
<td>-12.0</td>
<td>-14.8</td>
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<table>
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<tr>
<th>GS 236-0103: STB vs. ATV + RTV + FTC/TDF</th>
<th>STB ≥50 yrs (n=48)</th>
<th>STB &lt;50 yrs (n=305)</th>
<th>ATV+RTV +FTC/TDF ≥50 yrs (n=48)</th>
<th>ATV+RTV +FTC/TDF &lt;50 yrs (n=307)</th>
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<td>Efficacy</td>
<td>94%</td>
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<td>Mean CD4 increases cells/mm³</td>
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<td>AEs</td>
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<tr>
<td>-AEs leading to DC</td>
<td>2.1%</td>
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<tr>
<td>-Serious AEs</td>
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<td>Median Changes in eGFR mL/min</td>
<td>-10.2</td>
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3rd International Workshop on HIV & Aging

5-6 November 2012, Baltimore, MD, USA

Abstracts

Poster Presentations
Abstract: P_01

Neurology

Could changes in cognition be quantified clinically using a combination of patient-reported and performance-based measures?

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Background: Given the high prevalence of HIV-Associated Neurocognitive Disorders (HAND), evaluation of cognition should be an integral part of routine clinical care. In particular, documenting a decline in cognition over time has important clinical implications. Questionnaires eliciting cognitive symptoms are easily applicable but their clinical significance is unclear. Performance-based measures are thought to be a better indicator of cognitive function. The extent to which both approaches assess the same construct remains to be determined. This study is the first step towards the development of a tool that would reliably measure cognitive ability in a few questions, using modern psychometric methods. Its objective was to estimate the extent to which a calibrated measure of cognition, which combines items of patient-reports and performance–based items, form a hierarchical unidimensional construct by using Rasch modeling.

Methods: Cognition was assessed in 76 non-demented HIV+ individuals using both performance-based measures (the Montreal Cognitive Assessment (MoCA) and a brief computerized battery), as well as three self-report measures (PDQ, MSNQ and FRSBE). The items were combined and Rasch analyzed to create a measure of ‘cognitive ability’.

Results: The final measure had good statistical fit to the Rasch model, and covered 7 logits (or s.d.) of the theoretical construct, with items ranging from -3.5 to +3.5 logits (target is -4 to +4). It included several performance-based items as well as patient-reported items, demonstrating that both approaches measure the same underlying latent construct. Items covered the following cognitive domains: language, memory, speed of information processing, executive function/ abstraction, attention/working memory. Some patient-reported items reflected the highest level of cognitive ability, potentially explaining some of the discordance between patient reports and objective measures.

Conclusion: This type of measure, which quantifies on the same scale cognitive ability using both patient-reported and performance-based cognitive measures is completely novel. It allows clinicians and researchers to understand the mathematical relationship between these two concepts. It permits quantification of cognitive complaints, thereby facilitating clinical documentation of cognitive ability. The fit of the data to the Rasch model supports a relatively straightforward approach to the measurement of cognition as a global construct, in which cognition is evaluated across an appropriate range of difficulty rather than across several distinct cognitive abilities. It also paves the way to the development of an adaptive measure that would allow clinicians to reliably quantify changes in cognition using a few questions that could be administered in less than 15 minutes.

No conflict of interest

Abstract: P_02

Telomerase expression, activity and function in mouse cortex and cerebellum during normal aging and in neurodegenerative diseases

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Results: The final measure had good statistical fit to the Rasch model, and covered 7 logits (or s.d.) of the theoretical construct, with items ranging from -3.5 to +3.5 logits (target is -4 to +4). It included several performance-based items as well as patient-reported items, demonstrating that both approaches measure the same underlying latent construct. Items covered the following cognitive domains: language, memory, speed of information processing, executive function/ abstraction, attention/working memory. Some patient-reported items reflected the highest level of cognitive ability, potentially explaining some of the discordance between patient reports and objective measures.

Conclusion: This type of measure, which quantifies on the same scale cognitive ability using both patient-reported and performance-based cognitive measures is completely novel. It allows clinicians and researchers to understand the mathematical relationship between these two concepts. It permits quantification of cognitive complaints, thereby facilitating clinical documentation of cognitive ability. The fit of the data to the Rasch model supports a relatively straightforward approach to the measurement of cognition as a global construct, in which cognition is evaluated across an appropriate range of difficulty rather than across several distinct cognitive abilities. It also paves the way to the development of an adaptive measure that would allow clinicians to reliably quantify changes in cognition using a few questions that could be administered in less than 15 minutes.

No conflict of interest
Background: TERT the catalytic subunit of telomerase is expressed in neonatal brain and in distinct regions of adult brain, and was shown to protect neurons from apoptosis. We previously showed the expression and activity of telomerase in the adult mouse cerebellum and cortex. In addition, increasing its level exerts neuroprotection in vitro and in vivo.

Material & Methods: 8 old (20-24 month) and 10 young (2-3 month) CD1 mice were used for this study. TERT expression was measured by real-time PCR, Western blot and immunestaining telomerase activity was measured by TRAP assay. TERT knockdown motor neuron-like cells (NSC34) were generated by infecting the cells with lentivirus that contains TERT shRNA. Cell viability was measured by XXT assay, mitochondrial membrane potential (MMP) was measured by TMRM assay and the ROS level was measured by DCFH-DA assay.

Results: Telomerase is found in the nucleus, cytoplasm and also attached to the DNA. In old mice (20-24 month) cerebellum and cortex the fraction of TERT in the cytoplasm is increased significantly while the fraction of DNA-bound TERT is reduced compared to young mice. Surprisingly, telomerase activity shows the opposite picture, it reduced in the cytoplasm and increased in the DNA-bound protein extract. Preliminary results suggest that the incoherence between telomerase expression and activity is a result of a yet unknown DNA-bound telomerase inhibitor.

We hypothesized that telomerase role in neuronal aging is mediated by its non-canonical activities in the mitochondria which reduce the cellular sensitivity to oxidative stress, which is a major cause of brain aging. We found for the first time that TERT is located in purkinje neurons dendrites in association with the mitochondria. Its localization in such a long distance from the nucleus is intriguing.

TERT knockdown cells are significantly more sensitive to H2O2 challenge than wild type cells. This increase in sensitivity was accompanied by a reduction in ATP levels and increased rate of mitochondrial membrane potential collapsing in response to adding of mitochondrial uncoupler and increased expression of catalase and sod1. TERT knockdown neurons exposed to H2O2 challenge exhibit increased ROS production and reduced the ability to induce the expression of the antioxidant enzymes catalase and sod1 above their basal level.

Conclusions: The differences in telomerase expression and activity during aging suggest that it has a role in neuronal aging, even though neurons are non-dividing, fully differentiated cells. Our results indicate that telomerase has the ability to improve mitochondrial functionality and antioxidant response in neurons. This ability of telomerase can explain its protective role during normal neuronal aging and in neurodegenerative diseases.

Abstract: P_03

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

Evidence informing the intersection of HIV, aging and health: A scoping review

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Background: The intersection of HIV, aging and health is an urgent issue globally due to the growing number of people over age 50 with HIV, which includes both those who are newly infected and long-term survivors. Given this trend, research, policy, and practice must adapt to the ‘greying’ of HIV by developing a more comprehensive understanding of the health impacts of HIV in older individuals.

Material & Methods: We conducted a scoping review of peer-reviewed and grey literature
published since 1996 to explore the impacts of aging on the health of older PHAs (50 years or older). We conducted electronic database searches, internet searches, and manual searches of literature on the topics of older people living with HIV and health, and solicited recommendations from key experts. To determine inclusion, each reference was reviewed independently in duplicate; any reviewer disagreements were resolved by consensus or by a third independent reviewer. We focused our analysis on six domains: physical health, mental health, sexual health, adherence, health service access, and social participation.

Results: After reviewing 9,231 references, we included 204 studies: two systematic reviews, 172 quantitative studies, 25 qualitative studies, and 5 mixed methods studies. Of these, 160 were conducted primarily or exclusively in the United States (78%). Other jurisdictions amply represented include: Italy - 11 studies (5%), United Kingdom - 10 (5%), Spain - 9 (4%), France - 7 (3%), Canada - 4 (2%), and Brazil 4 (2%). Fifty-one percent (n=104) of these studies were published since 2007. Although the majority of the studies derived their samples from the general community or clinical populations, study samples were disproportionately men who identified as gay or bisexual or whose HIV-exposure category was classified as MSM. Most of the included literature addressed physical health (n=100), followed by mental health (n=59), social participation (n=39), adherence (n=38), health services (n=34), and sexual health (n=19). Health topics addressed in the literature include HIV- and aging-related co-morbidities (i.e., cancer, cardiovascular diseases, diabetes, renal functioning, and musculoskeletal concerns), mortality, opportunistic infections, neurocognitive functioning and impairment (e.g., HIV-associated neurocognitive disorders), mental health conditions (e.g., depression), psychological well-being/resilience, social supports, ageism and stigma, antiretroviral adherence, health care utilization/access, and sexual risk behaviours.

Conclusions: The number of primary studies and systematic reviews yielded from this review suggests that the topic of HIV in older people is an emerging area of research, particularly in high-income countries. The methods used in examining older age, HIV and health tend to be quantitative in nature and focus on the deterrents or risks associated with older age and seropositivity. We recommend that future research take a broader view of health, and also look at positive health from a strength-based or wellness perspective. Additionally, the diversity of people living with HIV warrants research examining aging from diverse perspectives (i.e., geographic location, gender identity, socioeconomic status, ethnicity, race and sexual identity/orientation).

This paper was presented at the 41st Annual Scientific and Educational Meeting of the Canadian Association of Gerontology Conference (CAG2012), Vancouver, BC on October 20, 2012.

No conflict of interest

Abstract: P-04

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

Aging with HIV in Tanzania

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Background: The increase in life expectancy of HIV infected patients, following the scale-up of ART, raises concern of a potential overlap between HIV and non-communicable diseases (NCDs) epidemics in sub-Saharan Africa. Population will age, 'unmasking' the burden of NCDs, previously hidden due to high rates of HIV-related mortality. NCDs are becoming more important in low- and middle income settings, where prevalence of risk factors is high and prevention efforts are limited.
Objective: The objective of the study is to assess the prevalence and risk factors for non-communicable diseases among HIV-infected patients, compared with matched controls in a rural area in Tanzania.

Methods: Cross-sectional observational study of 178 ART-exposed HIV-infected patients receiving first line ART with Triamune®, and 71 healthy HIV-uninfected controls, enrolled at the CTC and VCT of Usokami health Centre, Mufindi District -Tanzania.

The following were the indicators for each NCD recorded at the time of clinical visit:

- Diabetes (T2DM): fasting blood glucose>126 mg/dL,
- Hypertension (HTN): Systolic/diastolic blood pressure>140/85 mmHg,
- Cardiovascular events (CVE): assessed with ECG, COPD assessed with a portable spirometer (Easy One Diagnostic) using the FEV1/FVC cut off <70%,
- Chronic Kidney Disease (CKD): e-GFR <60 mil/min using MDRD formula.

Polipathology (Pp) was defined as the association of two or more NCDs.

Results

Two-hundred-forty-nine individuals were included: cases and controls were well balanced (p=0.50) for gender (males 41.57% vs 43.66) and age (38.61 vs 38.61 years). Smoke habits was rare (11.8%) in both groups but indoor air pollution exposure from cooking with solid fuels was common (29.7%). HIV infected patients were thinner (BMI= 21.7±3.4 vs 24.7±4.3, p<0.001), with lower waist circumference (80.8±6.9 vs 85.4±10.5, p<0.001), and with a higher burden of past TB disease (14.4% vs 4.23%, p=0.027).

HIV infected individuals had a median nadir and current CD4 respectively of 222/microL (IQR=112-301) and 351/microL (IQR=236-502). Median ART exposure was 26.4 (IQR=12.5-39.7) months.

Prevalence on NCD was similar in the two groups. In particular: COPD: 25.99% vs 12.86%, p=0.025; T2DM: 27.85% vs 27.69%, p=0.981; CVE: 0.56% vs 2.82%, p=0.141; HTN: 56.18% vs 66.2%, p=0.147; CKD: 0.56% vs 0%, p=0.527. Pp prevalence was 22% vs 25.3% with no statistical difference in three different age strata (<30, 31-45, >46 years).

Independent associated factors with Pp were analyzed using multivariable logistic regressions. Variables included were: age strata, sex, CD4 nadir (we assumed HIV-negative had >200 cell/µL), and HIV infection. The age strata ≥46 years resulted the only factor associated with Pp (OR 2.96, 95% C.I. 1.07; 8.21). The same model was repeated in the HIV subset including ARV exposure and current CD4 but no variable resulted associated with Pp.

Conclusions: In this young population with little exposure to ARV the burden of NCD is high, although not different from aged match controls. The cross-sectional nature of our study do not avoid a possible survival bias in our population. The detected high prevalence of NCD have broad and important consequences for the organization of health-care services and suggesting the need for an integrated care of both HIV infected and uninfected individuals.

No conflict of interest

Abstract: P_05

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

Older age, but not antiretroviral therapy, is associated with urine prostaglandin E2 metabolite increases in HIV-infected women with central adiposity

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Background: Eicosanoids are arachidonic acid breakdown products that can be quantified in urine as surrogate measures of oxidant stress.
and vascular health. Abnormal eicosanoid levels have been reported in HIV-infected persons, and may vary by sex, anthropometrics and other metabolic parameters. Raltegravir (RAL), an HIV-1 integrase inhibitor, has demonstrated limited metabolic effects in short-term follow-up. The Women, Integrase, and Fat Accumulation Trial (WI-FAT) was designed to assess the effect(s) of switching a PI- or NNRTI-based ART to RAL on visceral adipose tissue (VAT) in women with abdominal adiposity. This analysis describes the effects of a switch to RAL on urine eicosanoids in WI-FAT subjects.

**Material & Methods:** Women with HIV-1 RNA <50 copies/mL, stable ART including 2 NRTIs (tenofovir or abacavir and emtricitabine or lamivudine) plus a PI or NNRTI, and central adiposity (waist circumference >94cm or waist:hip >0.88) were enrolled at five centers in North America from September 2008-July 2010 and randomized to switch their PI/NNRTI to RAL (immediate arm) or continue present ART for 24 weeks (delayed arm). F2-isoprostanes (F2-IsoP), and prostaglandin E2 (PGE-M), prostacyclin (PGI-M), and thromboxane B2 (TxB2) urine metabolites were quantified at baseline and week 24 using gas or liquid chromatography-mass spectroscopy. Analyses included Spearman correlations, paired t test, and/or Wilcoxon signed rank tests. Generalized linear models assessed associations between eicosanoid changes and study arm, adjusting for baseline PI use, body mass index (BMI), smoking status, and age (≥50 vs. <50 years).

**Results:** Thirty-seven women completed Week 24 (immediate arm= 17; delayed arm=20). Groups were similar at baseline, with median age 43 years, BMI 32 kg/m², and 23 (62%) receiving a PI (17 ritonavir-boosted PI). Women in the delayed arm were more likely to smoke (58% vs. 24%; p=0.03). Baseline median (IQR) urine F2-IsoP, PGE-M, PGI-M, and TxB2 (ng/mg creatinine [cr]) was 2.14 (1.49, 3.16), 8.06 (4.47, 10.56), 0.10 (0.06, 0.15), and 0.46 (0.25, 0.73), respectively. Baseline PGI-M was significantly lower in the immediate arm (p=0.005), and remained lower at week 24 (p=0.04); no other cross-sectional differences were observed between arms. Over 24 weeks, TxB2 increased in the immediate vs. delayed arm (+0.09 [-0.04, +0.13] vs. -0.02 [-0.20, +0.03]; between group p=0.06), but did not correlate with VAT change.

In the delayed arm, 24-week VAT change positively correlated with PGI-M (rho=0.45; p=0.04), with a trend seen for PGE-M (rho=0.41; p=0.07). In an adjusted model, age ≥50 years (N=8) was associated with 24-week PGE-M increase, independent of study arm (β=8.3 [95% CI 0.3, 16.3]; p=0.04).

**Conclusions:** In these HIV-infected women with central adiposity who were well controlled on ART, switching Pi- or NNRTI-based ART to RAL did not have significant effects on urine eicosanoids over 24 weeks. In subjects continuing PI or NNRTI, increased VAT marginally correlated with increased PGI-M and PGE-M. Older age (≥50) at entry was independently associated with an increase in PGE-M, a complex biomarker previously associated with pro-inflammatory states (malignancies in HIV-uninfected populations and HIV viremia in Haitian women). The influence of aging on eicosanoids during HIV-infection requires further study.

No conflict of interest

**Abstract: P_06**

**Geriatrics and clinical care**

**HIV Testing Among Californians Aged 50-64: A Descriptive Analysis**

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**Objective:** Testing is critical for the prevention and care for the spread of HIV-1 among older adults, aged 50-64. The overarching goal of the research question was to determine some of the reasons adults age 50 and older were not routinely tested for HIV in California in 2010.
**Methods:** Secondary data analysis directed from the 2010 edition of the Behavioral Risk Factor Surveillance System (BRFSS) formed the basis for this project. The surveyed adult populations were between ages 50-64 years living in California who completed the core module. The risk and demographic characteristics of the age 50-64 population were obtained from the BRFSS survey. Data analysis examined whether adults age 50 and older were ever tested for HIV in California. SAS 9.3 statistical software was used for categorical data, by Chi-Square ($\chi^2$) Test Statistics.

**Results:** In 2010, 5,544 individuals aged 50-64 years were residents of the state of California who responded to the BRFSS survey. The outcome of interest, ever tested for HIV group, contained ~30% of the sample of ages 50-64 years. The ever tested group had the following characteristics: (a) female (55%); (b) completed a college degree or higher (48%), had some college (28%), completed high school (14%), or did not complete high school (9%); (c) White, non-Hispanic (71%), Hispanic (16%), Unknown (8%), and Black, non-Hispanic (6%); (d) Higher income levels (~58%); and (e) Low risk groups (97%). The findings also show there were significant differences in distribution of HIV tests by sex, education, race/ethnicity, income, and HIV risk groups (p value<0.0001).

**Conclusion:** Currently there is a growing need for continual analysis, appropriate health education and health promotion efforts to increase HIV testing and to promote disease prevention among 50-64 years adults; a group that perceive themselves as low-risk for HIV infection in California.

*No conflict of interest*

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**Abstract: P_07**

**Geriatrics and clinical care**

**What is the difference in the cardiovascular risk in the ageing HIV cohorts compared to the general population? - QRISK®2; a pilot study, UK.**

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**Background:** The HIV population is living longer with the advent of highly active antiretroviral therapy (HAART). HIV, ageing, HAART and increased body mass index (BMI) are associated with increased risk of cardiovascular events. The QRISK-2011 score is a validated tool that estimates the risk of a person developing cardiovascular disease (CVD) over the next 10 years in England. The aim of our pilot study is to estimate the risk of CVD over the next 10 years in our HIV cohort over the age of 55 compared to the general population using the QRISK®2 algorithm[1].

**Methods:** Data of HIV patients over the age of 55 in our cohort are extracted and analysed. Patients who had cardiovascular events were excluded from our study. Patients’ QRISK2 scores between January and June 2012 were calculated using the online calculator at: http://qrisk.org/. The score of a typical person with the same age, sex, and ethnicity were also recorded.

**Results:** There were 23 male and 7 female patients. (Mean age 61 years, 20 heterosexuals, 9 homosexuals, 1 bisexual; 16 Caucasians, 12 Blacks, 1 Chinese, 1 Indian). The mean CD4 count at diagnosis of HIV was 166 cells/cu³ with a median of 120 cells/cu³ (Range 6 - 680 cells/cu³). All of the patients are on antiretroviral treatment. The mean BMI of our study cohort was 27.1 compared to 28 in the general population. The average QRISK % in our cohort was 18.4% with a median of 13.5%. In the
general population with the same age, sex and ethnicity, it was 12.6% with a median of 11.2%. Eight patients (26.6%) have a high QRISK score >20% vs. 4 (13.3%) in the general population. 23 (77%) of our cohort had a higher risk compared to the general population. The mean relative risk our cohort developing CVD was 1.7 with a median of 1.35 compared to the general population.

**Summary: CVD is a major cause of mortality in the world and has particular significance in the ageing HIV cohort. Our ageing HIV cohort has fewer overweight and obese patients (60%) than the general population (80%) in England, yet the CVD risk is higher. (Mean 18.4% vs. 12.6; Median 12.6% vs. 11.2%). A quarter of our cohort have a high QRISK score of >20% compared to a sixth in the general population. Despite the fact that the QRISK® algorithm does not take into account a persons HIV status and their treatment for HIV, overall our HIV cohort have higher risk scores. This study highlights that clinicians managing HIV patients should be alert to the increased CVD risks and manage the patients accordingly. The CVD risk of HIV patients on HAART is doubled compared to HIV positive treatment naïve individuals[2]. How should clinicians adjust the QRISK score to reflect the increased risks?

We are in the process of starting a large multi-centre HIV cohort study to confirm our findings and identify the correction factor to adjust the QRISK % for the HIV population in England.


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**Abstract: P_08

Geriatrics and clinical care

Menopause in HIV-infected women: somewhat different?

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**Background:** Menopause is a physiological aging, process. This complex biological process, involving both physical and psychological health, appears to be an appropriate setting where to study aging in people living with HIV. Some studies have found that HIV was independently associated with earlier onset of menopause, hypothesising an increased risk for medical illness and mortality as well as a higher burden on menopausal symptoms. Little is known on menopausal symptoms in HIV infected women. The objective was to describe prevalence of clinical diagnosed comorbidities, polyopathy (Pp) and patient related outcomes (PROs) domains in HIV infected patients on menopause.

**Materials & Methods:** Multi-central, cross sectional study including HIV-infected women in menopause or pre-menopause. Menopause was retrospectively diagnosed using WHO criteria of 12 months of amenorrhoea without any pathological cause. The following comorbidities were investigated: T2DM, hypertension, cardiovascular disease, osteopenia, renal and hepatic failure, hypotiroidism, malignancies. Pp was defined as the association of two or more comorbidities. The following questionnaire were administered by phone and vis-a-vis:

- MenQoL: a Menopause-Specific Quality of Life Questionnaire validated in HIV-negative population exploring vasomotor symptoms,
mental health, physical health, sexual well-being domains.
- CESD-10 exploring depression
- Physical and psychological health quality of life perception
- Fragility perception
- Cognitive function perception
- Aging perception

Results: One-hundred-ten women were included: 61 in the menopause group and 49 in the pre-menopause group. Median age at menopause was 47.5 years (SD=3.9). Using this exact age of menopause onset, it was projected that 87% of the cohort will be in menopause by 2015.

Demographical and clinical data: No differences (p=ns) were found in menarche (12.9 vs 12.6 yrs), education (university= 8.2 vs 8.16%), housing situation (alone=24.6 vs 18.4%), risk factors (smoke =50 vs 38.8%, oral contraceptives use= 16.4 vs 10.2%), term pregnancy (60.7 vs 46.9%) and abortion (62.3 vs 59.2%) in menopause compared to no-menopause group. Differences were found in numbers of children (2 vs 1, p=0.008) and screening access: mammography (82 vs 55.1%, p=0.004) and faecal occult blood (37.7 vs 18.4%, p=0.035).

Comorbidities: A trend towards a higher polypathology rate was found in menopause compared to no-menopause group, respectively 38.33% and 28.26% (p=0.307).

PROs: MenQol questionnaire showed a significant higher prevalence of vasomotor (2 vs 3, p=0.034), physical (2.25 vs 3.81, p<0.001), psychological (2.87 vs 4.14, p=0.001) and sexual (1.67 vs 4.33, p<0.001) domains. Physical health perception 67% (IQ 60-80) vs 87% (IQ 70-95) and mental health perception 73% (IQ 50-90) vs 89% (IQ 60-90) were worse in the menopause group (p=0.0002 and p=0.0251, respectively). A trend for higher fragility perception (16% vs 26%) and depression (29% vs 39%) was shown without reaching statistical significance.

Conclusions: HIV cohort have a rapidly increasing number of women entering in menopause. An expected increase prevalence of Pp in menopause women is confirmed in this study. HIV-infected women in menopause report worse PROs domains, including: vasomotor symptoms, mental health, physical health, sexual well-being, depression. MenQol appeared to be an appropriate tool to estimate the physical and psychological health of HIV infected women in menopause.

No conflict of interest

Abstract: P_09

Geriatrics and clinical care

Determinants of clinician knowledge on aging and HIV/AIDS: a survey of practitioners and policy makers in Kampala District, Uganda

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Background: The HIV/AIDS epidemic has evolved with an increasing burden in older adults. We assessed for knowledge about aging and HIV/AIDS, among clinicians in Kampala district, Uganda.

Materials & Methods: A cross-sectional survey of 301 clinicians complemented by 9 key-informant interviews between May and October 2011. Data was analyzed by multivariable logistic regression for potential determinants of clinician knowledge about HIV/AIDS in older adults, estimating their adjusted Odds Ratios (aOR) and 95% confidence intervals (95% CI) using Stata 11.2 software.
Results: Two-hundred and sixty-two questionnaires (87.7%) were returned. Respondents had a median age of 30 years (IQR: 27 – 34) and 57.8% were general medical doctors. The mean knowledge score was 49% (range 8.8% – 79.4%). Questions related to co-morbidities in HIV/AIDS (non-AIDS related cancers and systemic diseases) and chronic antiretroviral treatment toxicities (metabolic disorders) accounted for significantly lower scores (mean, 41.7%, 95% CI: 39.3% – 44%) compared to HIV/AIDS epidemiology and prevention (mean, 65.7%, 95% CI: 63.7% – 67.7%). Determinants of clinician knowledge in the multivariable analysis included (category, aOR, 95% CI): clinician age (30 – 39 years; 3.28: 1.65 – 9.75), number of persons with HIV/AIDS seen in the past year (less than 50; 0.34: 0.14 – 0.86) and clinical professional (clinical nurse practitioner; 0.31: 0.11 – 0.83).


Conflict of interest
financial relationship(s): EAO is a Research Scholar at the JCRC Uganda, Uganda – Case Western Reserve University Research Collaboration, supported by the Fogarty International Clinical Research Scholars and Fellows Program at Vanderbilt University (R24 TW007988) and the American Relief and Recovery Act, Fogarty International Centre, National Institutes of Health, USA.

Abstract: P_10

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

Meta-analysis comparing the safety, tolerability, and efficacy of Lopinavir/ritonavir-containing antiretroviral therapy in subjects aged <50 versus ≥50 years from randomized clinical trials

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Background: Antiretroviral therapy (ART) has dramatically increased survival of HIV-infected patients, with estimated life expectancy approaching that of the non-HIV-infected population. Data describing the safety and efficacy of ART in HIV-infected patients aged ≥50 years are limited. This meta-analysis compared subjects aged <50 and ≥50 years receiving lopinavir/ritonavir (LPV/r)-containing ART to evaluate the potential effect of age on safety, tolerability, and efficacy.

Materials and Methods: Trials were included based on the following criteria: Abbott or AIDS Clinical Trials Group (ACTG) randomized clinical trials conducted in adult subjects, LPV/r 800/200 mg/day as part of a 3-drug regimen, and follow-up duration ≥48 weeks. A random-effects meta-analysis was performed to evaluate virologic efficacy; analyses of other endpoints were performed using “pooled” data from individual trials.

Results: 2608 subjects from 10 RCT were included; age ranged from 17-84 years, with 2248 (86.2%) subjects <50 (mean age 36.2) and 360 subjects (13.8%) ≥50 (mean age 55.7) years old. Age groups were similar with respect to gender, race, ethnicity, mean HIV-1 RNA and mean CD4+ T-cell count at baseline (P≥0.505). 77.4% and 74.7% of subjects were ART-naïve in the <50 and ≥50 age groups, respectively (P=0.280). For those subjects with post-baseline laboratory data, significant differences were
observed between the <50 and ≥50 groups, respectively, in baseline mean values for amylase (81.3 and 93.9 U/L), lipase (38.7 and 50.8 U/L), creatinine clearance (117.1 and 95.7 ml/min), cholesterol (4.2 and 4.4 mmol/L), glucose (4.9 and 5.5 mmol/L) (P<0.001 for all), and aspartate aminotransferase (34.9 and 38.7 U/L, P=0.010). Virologic responses were similar at week 48 (figure): 64.9% and 67.8% of subjects <50 and ≥50 years, respectively, had plasma HIV-1 RNA <50 copies/ml (meta-analysis P=0.992; intent-to-treat non-completer=failure analysis). Mean change from baseline in CD4+ T-cell count was significantly different between subjects <50 years and ≥50 years (+193.9 and +163.5 cells/µL; P=0.001). Overall discontinuation rates were similar; however, smaller proportions of subjects <50 discontinued due to AEs/HIV-related events (4.9% versus 9.4%, P=0.001) and reported moderate-to-severe treatment-related AEs (30.5% versus 36.4%, P=0.027) compared to subjects ≥50, specifically hypercholesterolemia (1.6% versus 4.4%, P=0.001) and hypertriglyceridemia (3.5% versus 6.4%, P=0.012). Statistically significant between-age group differences in the proportion of subjects with post-baseline grade 3+ clinical laboratory abnormalities were observed for amylase (2.5 % versus 6.4%, P=0.002), lipase (2.9% versus 7.7%, P<0.001), cholesterol (5.1% versus 10.2%, P<0.001), glucose (1.2% versus 3.5%, P=0.013), and creatinine clearance (1.3% versus 9.4%, P<0.001).

Conclusions: No significant difference was observed in virologic response between subjects <50 and subjects ≥50 years old receiving LPV/r-containing ART. Mean increase in CD4+ T-cells was smaller for the ≥50 year-old group. Greater proportions of older subjects reported AEs and discontinued therapy due to AEs/HIV-related events. A greater proportion of subjects aged ≥50 years had post-baseline grade 3+ laboratory abnormalities in amylase, cholesterol, glucose, and creatinine clearance; however, there were significant differences between age groups in baseline values for these parameters. This meta-analysis suggests that LPV/r-containing regimens have comparable safety, tolerability, and efficacy in subjects <50 and ≥50 years old through 48 weeks of treatment.

Conflict of interest: The design, study conduct, and financial support of the clinical trial was provided by Abbott. Abbott participated in the interpretation of data, review, and approval of the poster. The presenting author is an Abbott employee and may hold stock or options.
Abstract: P_11

Less resilient older HIV-infected persons evidence instrumental activities of daily living declines

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Background: By 2015, it is estimated that adults 50 years old and older will make up approximately half of all individuals with HIV/AIDS in the United States (Sankar et al., 2011; Effros et al., 2008). As persons with HIV age, evidence is emerging that older HIV-infected persons may be at increased risk for neurocognitive impairment and possibly subsequent declines in daily functioning (Thames et al., 2011). Moreover, it has been shown that HIV-infected individuals are less likely to identify as resilient (e.g., in areas of positive coping behaviors and social engagement) as compared HIV-uninfected persons (Kurts et al., 2012). The purpose of this preliminary study was to examine the relationship of resilience, neurocognitive functioning and instrumental activities of daily living (IADL) among older HIV-infected and uninfected individuals.

Method: Twenty-five (mean age=61.4) HIV-infected and 19 (mean age=58.8, p=0.35) HIV-uninfected participants completed a comprehensive neuropsychological assessment covering seven domains. Participants also completed questionnaires on resilience (Connor Davidson Resilience Scale-10 item), mood (Beck Depression Inventory-II), and daily functioning (Lawton and Brody Activities of Daily Living Questionnaire). Participants were classified as IADL dependent if they endorsed declines on several IADLs (e.g., financial management, medication taking), and indicated that the IADL declines were a result of neurocognitive problems.

Results: Results revealed that older HIV-uninfected individuals were significantly more likely to rate themselves as resilient (mean total score=31.2) as compared to HIV-infected persons (mean=26.0, p=0.04); however, the groups did not differ on level of neurocognitive functioning or depressive symptomatology. Additionally, HIV+ individuals who were IADL dependent tended to be less resilient compared to HIV+ IADL independent individuals and HIV-individuals (HIV+ IADL Dependent mean=20.3, SD=6.2; HIV+ IADL Independent mean=29.7, SD=5.6; HIV-uninfected mean=29.0, SD=8.5, p=0.07). HIV disease characteristics (i.e., current and nadir CD4 count, AIDS status, and detectable plasma viral load) did not differ between the HIV+ persons classified as IADL dependent or not.

Conclusions: Findings show that older HIV-infected persons report lower levels of resilience as compared to older HIV-uninfected persons. Moreover, lower levels of resilience among older HIV-infected individuals were associated with greater levels of IADL dependence. Given that HIV disease characteristics were comparable between the IADL dependent and independent groups, resilience may be an important determinant of daily functioning above and beyond HIV disease severity. More fully powered studies are needed to examine the association between resilience and daily functioning outcomes in the older HIV-infected population.

Abstract: P_12

Small Magnetite Antiretroviral Theranostics

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Background. Antiretroviral therapy (ART) has enabled HIV-infected people to live long productive lives. However, drug toxicities, compliance and limited penetrance into viral reservoirs have limited long-term ART efficacy. This will be compounded as infected people reach the sixth and seventh decades of life. Thus, our group is developing long-acting
nanoformulated ART (nanoART) to improve drug adherence and disease outcomes. A notable advantage of nanoART over native drugs rests in its potential to effect viral eradication. The recent development of small magnetite antiretroviral therapy (SMART) particles for theranostics (noninvasive assessment of drug distribution and disease diagnostics by magnetic resonance imaging, MRI) may assess ART particle distribution to viral reservoirs.

**Materials and Methods.** Poly(lactic-co-glycolic acid) (PLGA), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)2000] (DSPE-PEG2000) encased the SMART particle containing, atazanavir (ATV) and ultra small paramagnetic iron oxide (USPIO). These were dissolved in chloroform. Polyvinyl alcohol formed the emulsion that was sonicated to effect the optimal SMART size. After evaporating the organic solvent drug release from SMART was performed in isotonic saline. Cellular uptake and retention of the constituent iron and ART was performed in human monocyte-derived macrophages (MDM) for 8 hours. HPLC-UV/Vis and UPLC-MS/MS determined drug content. Magnetite and drug biodistribution was determined in male Balb/cJ mice after intravenous SMART injection (50 mg/kg ATV) and imaged by MRI over short (0-4 hours) or 24 hour times. For scan comparisons, T2 maps and a 3D spoiled gradient recalled echo image set (3D-GRE) were acquired prior to SMART injection. T2 maps were acquired continuously for the short intervals followed by a post injection 3D-GRE scan. CPMG phase cycled T2 mapping were used to quantify the T2 change linked to magnetite concentrations in tissue. The T2 weighted 3D MRI sequence was used to visualize signal loss indicating magnetite for both the short and 24 hour scans. This enabled determination of both drug and iron content of plasma and tissue.

**Results.** SMART particles were manufactured successfully with controlled drug/USPIO loading enabling a slow and sustained drug release (measured over hours to days) in saline and MDM. SMART particles were taken up efficiently by cells and retained over two weeks. In mouse proof of concept studies SMART T2 weighted images showed that iron concentrations over short intervals were largely due to vascular content. By 24 hours signal intensity was seen in liver and spleen with little to no iron in the kidneys. ATV levels in tissues directly correlated with MRI iron measures.

**Conclusions.** We posit that SMART particles can be developed for noninvasive evaluation of drug distribution and pharmacokinetics. The particles have the potential to permit evaluation of ART concentrations in viral reservoirs that include the brain and lymphoid tissues and provide rapid assessments of next generation cell and tissue ligand targeted particles.
3rd International Workshop on HIV & Aging

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