Ageing with HIV



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After 15 years into the era of potent combination antiretroviral therapy...

- Remarkable potential for sustained control of HIV infection
- Remarkable improvement in survival as a result of markedly reduced incidence of "infections and tumours" traditionally associated with HIV-related immunodeficiency
- With presumably increasingly better tolerated and less toxic ART regimens

As a result our patients with HIV are growing older and older...



% of patients

Data courtesy of Luuk Gras, HIV Monitoring Foundation

But....

Many cART-treated patients do not reach a normal lifespan...



Life expectancy in the current treatment environment may be as much as 10 to 30 years less than that in uninfected patients, particularly if cART is started late at a more advanced state of immunodeficiency

Prevalence of late presentation for persons presenting for care in 2008



Thanks to: ATHENA (F de Wolf) Brussels St Pierre Cohort (S deWit) Barcelona cohort (J Gatell) CHIC (C Sabin) ClinSurv HIV (O Hamouda) DHCS (F Engsig) EuroSIDA (J Reekie) FHDH ANRS CO4 (D Costagliola) ICONA (A d'Arminio Monforte) Swedish Cohort (J Brännström) SHCS (B Ledergerber)



HIV in Europe

*: 2007

Jens Lundgren, EACS 2009 Cologne

What do patients then get sick and die from?

 Diseases, each of which in the general population is known to be more prevalent in the elderly







Chronic liver disease





Osteoporosis & fractures







Chronic kidney disease

What do patients then get sick and die from?

- Diseases, each of which in the general population is known to be more prevalent in the elderly
- And there is increasing evidence that these morbidities known to be associated with ageing in general may be more prevalent in those with HIV, after adjusting for age and traditional risk factors...

Increased risk of myocardial infarction in HIV- infected patients in France, relative to the general population



"The higher relative risks of MI found in younger men and women in our study raises the possibility of a premature aging effect of HIV infection on the cardiovascular system"

Lang s et al. AIDS 2010, 24:1228-1230

Greater rate of fractures in HIV-infected versus uninfected individuals



Adapted from Triant VA et al. J Clin Endocrinol Metab 2008;93:3499–3504

Increased Risk of Some non-AIDS Cancers in HIV



non-AIDS cancer, by HAART era.

Shiels M et al JAIDS 2009;52: 611-22

Frailty in HIV

- Compared to HIV-uninfected men of similar age, ethnicity and education, HIV-infected men were more likely to have the frailty phenotype
- Frailty prevalence increases with longer duration of infection (risk 3–14 fold > in men infected with HIV for 4 to 12 years)
- The frailty prevalence for 55-year-old men infected with HIV for >4 years was similar to that of uninfected men >65 years old (3.4%)
- Lower CD4 count associated with frailty phenotype in HIV-infected patients, independent of ART use

So, in the setting of HIV these comorbid diseases not only may be more prevalent, but may also occur at earlier age

Could the ageing process be accelerated in HIV?



Assuming this is the case, which factors may be contributing to this process?

Pathogenesis of HIV-associated Comorbidities is Multifactorial

Modifiable lifestyle-related risk factors

Cell & tissue damage resulting in clinical comorbidity traditionally associated with ageing HIV-associated immune activation, and activation of Inflammatory and coagulation pathways

Antiretroviral toxicity

Age, gender, genetic factors

Nolan, Mallal & Reiss Sande's HIV & Aids Medicine 2nd Ed.2011 (in preparation)

Inflammatory & Coagulation Markers Are Higher In Treated HIV Disease than in HIV Seronegatives, Adjusted for Demographics and CV Risk Factors



Neuhaus J, et al. J Infect Diseases 2010





...Over the past decade, it has become widely accepted that inflammation is a driving force behind chronic diseases that will kill nearly all of us (Cancer. Diabetes and obesity. Alzheimer's disease. Atherosclerosis.)...

....Mediating inflammation in chronic diseases is a new frontier, its success still uncertain...

Chronic rheumatoid arthritis and increased CVD risk



Libby P. Am J Med 2008;121:S21-S31.

The immune regulation of bone remodeling



Schett, G. & David, J.-P (2010) The multiple faces of autoimmune-mediated bone loss *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2010.190



HIV Causes Disruption of the Gastrointestinal Tract





Biomarkers of Inflammation and Coagulation Activation associated with Mortality in HIV

Baseline Biomarker	Events (#)	OR (4 th /1 st QRT) Unadjusted	P-value
D-dimer	85	12.3	<0.001
IL-6	84	11.7	<0.001
sCD14	74	6.0	<0.001
hsCRP	85	2.2	0.047

Kuller et al PLoS Med 2008;5(10), Paton N IAS 2009 (#MOPEA034), Sandler CROI 2010 (#330), and unpublished data

Slide courtesy of Jason Baker

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Subcutaneous limb fat loss (lipoatrophy) with ZDV/3TC-containing ART (Mediclas Study)



van Vonderen MGA et al. PLoS One. 2009 May 21;4(5):e5647.

Proportion of subjects with $\geq 10\%$ and $\geq 20\%$ limb fat loss (ITT, primary endpoint)

% Limb fat loss from 0 to 96 weeks	TDF/FTC +EFV (n=56)	TDF/FTC +ATV/r (n=45)	ABC/3TC +EFV (n=53)	ABC/3TC +ATV/r (n=49)	Total (n=203)
≥ 10% Primary	14.3% (6.4%,25.3%)	15.6% (7.0%,28.6%)	18.9% (9.4%, 31.6%)	16.3% (7.5%, 28.8%)	16.3% (11.8%, 22.0%)
≥ 20% Post hoc	8.9%	0%	3.8%	6.1%	4.9%

 No statistically significant differences between NRTI components and NNRTI/PI components (Fisher's exact test)



Slide courtesy of Grace McComsey

Boosted Protease Inhibitors Differ in their Effects on Body Composition (BASIC Trial)

Visceral adipose tissue



S. Vrouenraets et al (manuscript submitted)



CO

HIV

CLINICAL CARE OPTIONS®

FRAM: Limb Muscle Mass, Central Adiposity, and 5-Yr Mortality in HIV+ Pts

- Multivariate regression analysis of 922 HIV+ pts, grouped in tertiles
- Low limb muscle mass, high central adiposity strongly associated with 5-yr mortality risk
 - Peripheral lipoatrophy not associated with mortality



Scherzer R, et al. CROI 2011. Abstract 76. Graphic used with permission.

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Results: Incidence Rate Ratios of Events

*Adjusted for baseline values of gender, ethnic origin, HIV risk group, region of Europe, HBsAg and HCV antibody status, prior AIDS, exposure to antiretrovirals, age, CD4 count, CD4 nadir, HIV-RNA viral load, date of baseline sample, season of sample and date of recruitment to EuroSIDA

JP Viard et al IWADRL 2010, London

HIV in itself as a pathogenic factor.... some recent examples.....

HIV-1 Tat protein enhances RANKL/M-CSF-mediated osteoclast differentiation Gibellini D et al. Biochem Biophys Res Commun. 2010

HIV Type 1 Alters Mesenchymal Stem Cell Differentiation Potential and Cell Phenotype ex Vivo Cotter EJ, Chew N, Powderly WG, Doran PP. AIDS Res Hum Retroviruses 2010

Circulating Nef induces dyslipidemia in simian immunodeficiency virus-infected macaques by suppressing cholesterol efflux Asztalos BF, et alJ Infect Dis. 2010



Metabolic Processes under CNS Control



Schett, G. & David, J.-P (2010) The multiple faces of autoimmune-mediated bone loss *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2010.190

Poly-pathology prevalence in cases and controls, stratified by age categories



Pp prevalence was higher in cases than controls in all age strata (all p-values <0.001) Pp prevalence seen in cases aged 41-50 was similar to that observed among controls aged 51-60 controls (p=0.282)

Implications for managing comorbidities

- Maintain HIV suppression
- Identify and appropriately manage traditional risk factors (smoking, blood pressure, BMI etc.)
- Try to optimize choice of antiretroviral regimen within the constraints of other issues:
 - ART history, archived resistance
 - Presence of active chronic hepatitis
 - Genetic factors (e.g HLA-B5701 positivity)
 - Need for specific concomitant medication
 - Etc etc
- Continue searching for least/non-toxic ARV regimens
- Novel interventions, including those modulating "inflammation"...

Prevention and Management

of Non-Infectious Co-Morbidities in HIV

European AIDS Clinical Society

Revised Edition to include section on Revised Edition anomanic of the section of

hivma

medicine association

mary Care Guidelines for the Management of Persons Infected with HIV

Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients

uiagnosis & wanagement of Disorders uiagnosis & wanagement of Disorders Neurocognitive HIV Associated Neurocognitive Guidelines for the Evaluation and Management of Dyslipidemia in HIV–Infected Adults **Receiving Antiretroviral Therapy**

Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers



Clinical

MIDSA hıvma Infectious Diseases

www.europeanaidsclinicalsociety.org

Ageing faster with AIDS in Resource-constrained settings

...the proportion of elderly people in Africa infected with HIV/AIDS is increasing. This increase brings both good and bad news:

good news because increased access to treatments means that patients are living with longer life expectancy; bad news because meeting the complexities of geriatric care for HIV-infected adults will further challenge overwhelmed health systems

Edward J Mills, Anu Rammohan, Niyi Awofeso; Lancet 2010



XIX INTERNATIONAL AIDS CONFERENCE JULY 22 - 27 WASHINGTON DC USA