AGEING AND HIV INFECTION.
Dr DC Spencer   Right to Care Helen Joseph Hospital
Johannesburg  South Africa   April 2016

Acknowledgements: Critical Care Options:
José R. Arribas, Hans-Jürgen Stellbrink.
ATHENA: Older Patients Becoming More Prevalent in the HIV-Positive Population

- **ATHENA**: Observational cohort of 10,278 HIV-positive pts in the Netherlands

- Modeling study projections:
  - Proportion of HIV-positive pts \( \geq 50 \) yrs of age to increase from 28% in 2010 to 73% in 2030
  - Median age of HIV-positive pts on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030

ATHENA: Comorbidities Increase With Age and With HIV Infection

Modeling study suggests that in 2030:

- **84% of HIV+ pts will have ≥ 1 NCD**
  - Increased from 29% in 2010
  - Pts with comorbidities higher in every age group in HIV+ pts vs uninfected

- **28% of HIV+ pts will have ≥ 3 NCDs**

- **54% of HIV+ pts will be prescribed meds other than ART**
  - Increased from 13% in 2010

- **20% will take ≥ 3 meds besides ART**
  - Mostly driven by increase in CVD

HIV-POSITIVE SUBJECTS REFERRED TO THE INFECTIOUS DISEASES UNIT, HELEN JOSEPH HOSPITAL, 2013-2015

N=1752 patients

Overall HIV-positive prevalence = 96.4% of patients seen by the ID service at the HJH.

Mortality in HIV+ve patients seen by the ID unit of the Helen Joseph Hospital

Age group | Number of Deaths (n) | Deaths (%)  
---|---|---
15-19yr | 2/40 | 5%  
20-29yr | 13/180 | 7%  
30-39yr | 73/691 | 10.5%  
40-49yr | 66/522 | 12.6%  
50-64yr | 29/277 | 10.5%  
≥65yr | 5/42 | 11.9%

Nel J, Ive P, Spencer DC. Infectious Diseases Database ID Department. Helen Joseph Hospital, Johannesburg, SA. April 2016

Whiteside A., Health Economics and HIV and AIDS Research Division (HEARD), University of KwaZulu-Natal. 2013
Comorbidities (%) in HIV-infected patients seen in the Infectious Diseases Programme, Helen Joseph Hospital, 2015

Non- Infectious Comorbid Conditions as a Percentage of the Total HIV Cohort (%)

- Hypertension
- Malignancy
- Chronic kidney disease
- Diabetes
- CVA
- Ischaemic heart disease

Age categories:
- Age < 20
- Age 20-29
- Age 30-39
- Age 40-49
- Age 50-64
- Age > 64

Nel J. Database. ID Department, Helen Joseph Hospital, Johannesburg, SA. April 2016
Kaiser Permanente: Life Expectancy in HIV-Infected vs Uninfected Persons

- Analysis of life expectancy in 24,768 HIV-infected and 257,600 HIV-uninfected adult pts in Kaiser Permanente California 1996-2011; 2 groups matched for age, sex, medical center, yr


Slide credit: clinicaloptions.com
## KP: Factors Contributing to Reduced Life Expectancy With HIV (2008-11)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Expected Yrs of Life Remaining at Age 20 Yrs</th>
<th>Difference (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HIV Infected and Began ART With CD4+ ≥ 500 cells/mm³</td>
<td>HIV Uninfected</td>
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<tr>
<td>Overall</td>
<td>54.5</td>
<td>62.3</td>
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<tr>
<td>No HBV or HCV</td>
<td>55.4</td>
<td>62.6</td>
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<td>No drug or alcohol abuse</td>
<td>57.2</td>
<td>63.8</td>
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<tr>
<td>No smoking</td>
<td>58.9</td>
<td>64.3</td>
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<tr>
<td>None of the above</td>
<td>59.2</td>
<td>65.0</td>
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</table>

**RESULTS:**
Estimated median survival time from age 50 years for HIV-infected individuals increased from 11.8 yr [95%CI: 10.2-14.5] during 1996-1999 to 22.8yr [95%CI:20.0-24.2] in 2006-2014.

Mortality Rate Ratios (MRRs) fell with increasing age from 3.8 [3.1-4.7] for those 50-55yr to 1.6 [1.0-2.6] for those 75-80 years of age.

Progression to AIDS or Death Within 5 Years of ART Initiation Increases With Age

- **Collaborative analysis of 12 HIV cohorts in US and Europe**
  - Assessed rates of progression to AIDS or death for pts with HIV-1 RNA ≥ 100,000 copies/mL, no previous AIDS-defining illness, and no history of injection-drug use

Reducing CVD Risk Factors Can Decrease Risk of CVD in Older HIV+ Patients

- Effective treatment of modifiable risk factors, such as smoking, cholesterol, and BP can significantly reduce an individual’s CVD risk

Model for Change in Relative Risk of CVD From Smoking Cessation, Reducing Cholesterol,* or Reducing Systolic BP† in a Cohort of 24,323 HIV-Positive Pts Without Prior CVD (D:A:D Study)

*Reduced by 1 mmol/L. †Reduced by 10 mm Hg.


**PREMATURE AGEING IN HIV PERSONS**

**More than ONE comorbid condition**

**Factors significantly associated with poly-pathology in HIV patients were**

- **Age:** per year increase, OR 1.11, 95%CI, 1.10-1.12
- **Male sex:** OR 1.77, 95% CI, 1.44-2.17, P<.001
- **Nadir CD4 count <200,** OR 4.46, 95%CI, 3.73-5.34, P<.001
- **Exposure to ART, per mth of exposure,** OR, 1.01, 95% CI, 1.001-1.019, P=.001

**Effect on age**

Expected age difference between patients (HIV+ve) and control subjects (HIV-ve) at which poly-pathology would be observed across a spectrum of odds ratios for Pp.

An approximately 10-15 year “earlier aging” phenomenon!!

**Figure.** The risk (probability) of poly-pathology (Pp) by age – as a continuous variable – for HIV+ve patients and uninfected controls in the cohort.

**Case-control study**

n=2854 patients, n=8562 control subjects

Modena University, Italy. 2002-2009. Age = 46yr (Mean)

Conclusion: Specific age-related non-infectious comorbidities and poly-pathologies were more common among HIV+ve group.

Across all age groups by strata, poly-pathology prevalence was significantly higher among patients (HIV+ve), compared with uninfected controls, *P*<.001.

<table>
<thead>
<tr>
<th></th>
<th>HIV+ve subjects</th>
<th></th>
<th>HIV-ve controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>≤40 yrs</td>
<td>80%</td>
<td>≤40 yrs</td>
<td>90%</td>
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<td>41-50 yrs</td>
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<td>42%</td>
<td>51-60 yrs</td>
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<td></td>
<td>≥60 yrs</td>
<td>31%</td>
<td>≥60 yrs</td>
<td>40%</td>
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</table>

**Numbers:**
- HIV+ve: N=542
- HIV-ve: N=1626

**Poly-pathology prevalence:**
- HIV+ve: 3.9%
- HIV-ve: 0.5%

**Legend:**
- No age-related comorbidity
- One comorbidity
- Two comorbidities
- Three comorbidities
- Four comorbidities

**Comorbidities assessed in this Study:**
- Cardiovascular
- Hypertension
- Renal disease
- Bone fractures
- Diabetes Mellitus Type II
NA-ACCORD: Immunologic but Not Virologic Response Decreased in Older Pts

- Analysis of pts who received initial ART with a boosted PI or NNRTI-based regimen in 19 cohort studies (NA-ACCORD; N = 12,196)

EVG/COBI/TDF/FTC: Pooled 96-Wk Efficacy by Age

- Analysis of 96-wk subgroup efficacy data from 2 randomized, double blind, active-controlled phase III studies

**RANDOMIZED CONTROLLED CLINICAL STUDIES**

Age does not appear to influence the response to ART

TAF vs TDF + EVG/COBI/FTC: Efficacy in Older Pts

- GS-US-292-0104/0111:

- Phase III trials in which treatment-naive pts, HIV-infected pts with estimated creatinine clearance of ≥ 50 mL/min were randomized to TAF (n = 866) or TDF (n = 867) coformulated with EVG/COBI/FTC

*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.


Estimated the mean CD4 cell count changes following the completion of 5 years of cART. N=892 patients

Of the CD4 cell count rates of change estimated, none was indicative of long term declines in CD4 cell counts

Of the yearly rates of change estimated for each level of the year-5 count and age interaction, none was found to be indicative of decreasing mean CD4 cell count change, even for the older patients who were aged up to 60 to 70 years. Nonetheless it is clear that some patients ARE experiencing declines in mean CD4 count over time viz. Stratum >750 CD4 and age >50yr.
The authors of the MACs study (below) indicate that equivalent patients differing only by age after 5-12 years of ART had significantly different long-term immunological outcomes.

Specifically older patients would need to initiate cART with a baseline CD4 count higher than younger patients to achieve the same levels of immunological reconstitution at 5-12 years on cART. This suggests that older HIV+ve patients experience smaller rates of change in their CD4 counts per year.

Li X, Margolick JB, Jamieson BD, et al. CD4 cell counts and plasma HIV-1 RNA levels beyond 5 years of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2011; 57: 421-428
FRAILTY AND THE AGEING HIV POPULATION

Despite receiving antiretroviral therapy middle-aged HIV infected men show reductions in exercise capacity, functional performance, physical activity and grip strength.

Figure. Reductions in aerobic capacity (VO2) in HIV-infected patients aged 30-80 years. Data on healthy subjects are shown in blue and data on HIV-infected patients are shown in red.

Fracture Prevalence Is Increased in Older HIV-Positive Pts

- 8525 HIV-infected pts compared with 2,208,792 uninfected pts in Partners HealthCare System

TAF vs TDF + EVG/COBI/FTC: Changes in BMD (GS-US-292-0104/0111)

TAF treatment was associated with smaller BMD loss than TDF treatment

Sub-study: BMD Changes With Immediate vs Deferred ART Over 3 Yrs

- Sub-study included 193 pts in early ART arm and 204 pts in deferred ART arm with f/u

- Greater BMD loss in hip and spine with immediate vs deferred ART
  - Estimated mean difference for hip: -1.5% (95% CI: -2.3% to -0.8%; P < .001)
  - Estimated mean difference for spine: -1.6% (95% CI: -2.2% to -1.0%; P < .001)

- Osteoporosis incidence similar between arms (P = .27)

## NRTI-Sparing or NRTI-Limiting Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Results</th>
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<tbody>
<tr>
<td>DRV/RTV + RAL (ACTG 5262)(^1)</td>
<td>Poor performance at high VL</td>
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<tr>
<td><strong>DRV/RTV + RAL (NEAT)(^2)</strong></td>
<td>Less effective at high VL, low CD4</td>
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<td>DRV/RTV + 3TC (switch study)(^3)</td>
<td>Small study; encouraging efficacy</td>
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<td><strong>DRV/RTV + MVC (MODERN)(^4)</strong></td>
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<tr>
<td>ATV/RTV + RAL (HARNESS – switch)(^5)</td>
<td>Less effective than standard ART</td>
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<td><strong>LPV/RTV + RAL (PROGRESS)(^6)</strong></td>
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<td>LPV/RTV + EFV (ACTG 5142)(^7)</td>
<td>Poorly tolerated but effective</td>
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<td><strong>LPV/RTV + 3TC (GARDEL)(^8)</strong></td>
<td>As effective as standard ART</td>
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<td>LPV/RTV + 3TC or FTC (OLE – switch)(^9)</td>
<td>As effective as standard ART</td>
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<td><strong>ATV/RTV + 3TC (SALT – switch)(^10)</strong></td>
<td>As effective as standard ART</td>
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ART Considerations for Pts With Bone Complications

• **DHHS considerations:**

  • Consider avoiding TDF: associated with greater decrease in BMD along with renal tubulopathy, urine phosphate wasting, and osteomalacia

  • Consider ABC/3TC

• Significantly greater BMD loss with PI-based regimens vs RAL-based regimens

• DTG + ABC/3TC associated with less bone turnover than EFV/TDF/FTC
Practical Challenges With ART
Use in Older Patients

• Comorbidities

• Poly-pharmacy
  • DDI, dosing, adherence challenges

• Renal or hepatic impairment
  • Alterations in pharmacokinetics, potential for drug toxicity

• Challenges with single-tablet regimens
  • Inability to alter single component dosing (ie, ABC or TDF) as needed

Acknowledgement: Critical Care Options: José R. Arribas, Hans-Jürgen Stellbrink.
Older patients were more frequently taking ART, had more frequently suppressed viral loads, and were more frequently taking non-ART co-medication.
### Additional Drug–Drug Interactions With ART

**EACS Guidelines. V7.1. November 2014.**

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<th>DRV/RTV</th>
<th>EFV</th>
<th>RPV</th>
<th>DTG</th>
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</table>

- **Orange**: No clinically significant interaction expected
- **Grey**: These drugs should not be co-administered
- **Blue**: Potential interaction that may require a dosage adjustment
- **Dark Blue**: Potential interaction predicted to be of weak intensity
## Drug–Drug Interactions With ART and Diabetes and Lipid-Lowering Therapy

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Contraindicated</th>
<th>Titrate Dose</th>
<th>No Dose Adjustment</th>
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<tr>
<td><strong>RPV</strong>[^1]</td>
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<tr>
<td><strong>EVG/COBI/FTC/</strong></td>
<td>Lovastatin Simvastatin</td>
<td>Atorvastatin Rosuvastatin</td>
<td>Atorvastatin Pitavastatin</td>
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<td><strong>DTG</strong>[^1,2]</td>
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<td>Metformin</td>
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<tr>
<td><strong>ATV/RTV</strong>[^1]</td>
<td>Lovastatin Simvastatin</td>
<td>Atorvastatin Rosuvastatin</td>
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<tr>
<td><strong>DRV/RTV</strong>[^1]</td>
<td>Lovastatin Simvastatin</td>
<td>Atorvastatin Pravastatin Rosuvastatin</td>
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<td><strong>EFV</strong>[^1]</td>
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<td><strong>RAL</strong>[^1]</td>
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<tr>
<td><strong>ATV/COBI or DRV/COBI</strong></td>
<td>Lovastatin Simvastatin</td>
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</table>

IMPACT OF AGING ON DRUG TOXICITY IN HIV-INFECTED PATIENTS

❑ Higher rates of **adverse medication effects**

❑ Ageing associated with **decreased hepatic cytochrome P450 activity** and **decreased renal tubular secretion and glomerular filtration**

❑ Age-related **body composition and physiological** changes affect drug PD and PK

❑ The elderly frequently use prescription and Over-the-Counter medications i.e. are exposed to **predictable and un-predictable drug-drug interactions**

❑ Concurrent **comorbidities are frequent:**
  • Metabolic, Renal and Cardiac
  • Tuberculosis, Fungal disease, infectious disease in the HIV-infected in Africa associated with poorer outcomes