Co-morbidities in HIV-patients: Hit hard, hit early?! 

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Life expectancy among PLHIV continues to increase over time

Expected age at death starting ART aged 20 years, by period of initiation*

![Graph showing life expectancy increase over time](image)

Men, second and third years of follow-up

Men, 3 years of follow-up

*Estimates of life expectancy were based on mortality during the first 3 years of follow-up and the second and third years of follow-up.
10y decreased life expectancy in older HIV+ adults in modern ART era

Denmark

Legarth et al. JAIDS, 2016

Ageing with HIV – with ARV therapy

Expected age at death

Men

Male UK life expectancy 78 years

May M et al. AIDS 2014;28:1193–1202

* Expected age at death for a person aged 35 years with different durations of ART according to current CD4 count and viral load suppression
Projected age distribution of HIV-positive patients in the Netherlands

<table>
<thead>
<tr>
<th>Patient’s age</th>
<th>2010</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 years</td>
<td>28%</td>
<td>73%</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>8%</td>
<td>39%</td>
</tr>
</tbody>
</table>


Non-AIDS illness burden in ageing PLWHIV

Disproportionately greater increases in prevalence of hypertension, dyslipidemia, CKD and CVD with ageing in PLWHIV

Palella FJ et al. CROI 2017. Seattle, WA. #663

HOPS cohort, 1997 to 2015
Proportion of PLWHIV with ≥1 NCD predicted to increase

- 2010: 29%
- 2030: 84%

Driven by

- CVD in 78%
- Diabetes in 17%
- Malignancies in 17%

Predicted burden of NCDs in PLWHIV 2010–2030*


Diagnosed On ART <50 copies Good health

90 90 90 90
Chronic inflammation is associated with increased risk for co-morbidities in HIV+ patients

Untreated HIV Infection

 Loss of immunoregulatory cells

 HIV replication

 Gut mucosal integrity ↓
 Microbial translocation ↑

 ART

 Reduced but persistent chronic inflammation, immune activation, elevated coagulation markers

 +

 Traditional co-morbidity risk factors, such as dyslipidemia, smoking, lipodystrophy, HTN, obesity, substance use

 Increased incidence of comorbidities and clinical disease

CVD risk in HIV-positive patients is beyond that predicted by traditional risk factors

Risk of heart disease is 1.5–2 times higher in HIV-positive patients, even after controlling for traditional risk factors

Grinspoon S. CROI 2015. Seattle, WA. Oral #O134
CVD risk in HIV-positive patients is beyond that predicted by traditional risk factors

Increased arterial inflammation in HIV

Aortic inflammation associated with ↑sCD163 levels (monocyte activation)
Arterial inflammation not directly driven by HIV (PET/CT)

Baseline

On ART

Inflammation

Lymph nodes

Aorta

Zanni et al. JAMA Cardiol 2016

CVD and HIV: Lipid-lowering therapies in patients with subclinical coronary plaques

N=40 PLWHIV, Atorvastatin versus placebo; 1-year double-blind trial
Mean Age ~ 50y, non-calciﬁed plaque by coronary CT angiography, LDL <130 mg/dL

Immune cell activation and systemic inflammation in MSM with HIV

<table>
<thead>
<tr>
<th></th>
<th>MSM HIV pos.</th>
<th>Healthy Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cell activation</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>T cell exhaustion</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>sCD163</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>FABP</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Monocytic activation markers</td>
<td>+++</td>
<td>-</td>
</tr>
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NRTI options are limited and not always guideline recommended

<table>
<thead>
<tr>
<th>Treatment considerations</th>
<th>TDF/FTC</th>
<th>ABC/3TC</th>
</tr>
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<tbody>
<tr>
<td>*High viral load1,2</td>
<td>Acceptable</td>
<td>Caution</td>
</tr>
<tr>
<td>High CVD risk1,2</td>
<td>Acceptable</td>
<td>Caution</td>
</tr>
<tr>
<td>Renal impairment2</td>
<td>Caution</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Decrease in BMD2,3</td>
<td>Caution</td>
<td>Acceptable</td>
</tr>
<tr>
<td>HLA-B*5701 positive1,2</td>
<td>Acceptable</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

* >100,000 copies/mL; BMD: bone mineral density; CVD: cardiovascular disease
** No viral load restriction for DTG/ABC/3TC use, according to May 2014 DHHS guidelines2

NRTI options without limitations?

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<tr>
<th>Treatment considerations</th>
<th>TAF/FTC</th>
<th>3TC only?</th>
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<tr>
<td>*High viral load\textsuperscript{1,2}</td>
<td>Acceptable</td>
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<tr>
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D:A:D: Cumulative exposure to ARVs associated with increased CKD\textsuperscript{*} risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>1 Yr</th>
<th>5 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>1.14 (1.10-1.19)</td>
<td>1.94 (1.57-2.39)</td>
</tr>
<tr>
<td>ATV + RTV</td>
<td>1.20 (1.13-1.26)</td>
<td>2.44 (1.86-3.21)</td>
</tr>
<tr>
<td>LPV/RTV</td>
<td>1.11 (1.06-1.16)</td>
<td>1.66 (1.32-2.09)</td>
</tr>
</tbody>
</table>

*Multivariate analysis. For each value, \( P < .0001 \)

*CKD: Chronic kidney disease

Maintenance of HIV therapy

Reactive

Proactive

Case series of 22 HIV-patients with TDF-associated proximal renal tubulopathy

Woodward CLN et al. HIV Medicine 2009
Faster progression of CKD in HIV-infected individuals as compared to HIV neg. controls

Kooij KW et al. JID 2017
Mixed model adjusted for age, sex, birth from African descent, hypertension, baseline CVD, cigarette smoking, chronic hepatitis C, T2D, dyslipidemia and their interaction with time

Dyslipidemia following switch from TDF to TAF

Lacey A et al. EACS 2017

n=110, dyslipidemia defined as per NCEP ATP III guidelines

HDL cholesterol and triglycerides: no changes
CVD risk prediction developed for the general population underestimate CVD risk in HIV+ patients

Observed vs predicted 5-year CVD outcomes in partners healthcare system


Innate immune activation predict mortality during suppressive ART

Hunt, JID, 2014  (see also: Sandler, JID, 2011; Tenorio, JID 2014)
If cytokines were colours,…

…what would be the right mixture?

Paul Cézanne

D:A:D: Traditional risk factors for CVD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Better RR (95% CI)</th>
<th>Worse RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Age per 5 yrs older</td>
<td></td>
<td>1.32 (1.23-1.41)</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>2.13 (1.29-3.52)</td>
</tr>
<tr>
<td>Previous CVD</td>
<td></td>
<td>4.64 (3.22-6.69)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>2.92 (2.04-4.18)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td>1.40 (0.96-2.05)</td>
</tr>
<tr>
<td>Diabetes (yes vs no)</td>
<td></td>
<td>1.86 (1.31-2.65)</td>
</tr>
<tr>
<td>Hypertension (yes vs no)</td>
<td></td>
<td>1.30 (0.99-1.72)</td>
</tr>
</tbody>
</table>

Multivariable Poisson model adjusted for age, sex, BMI, HIV risk, cohort, calendar year, race, family history of CVD, smoking, previous CVD event, TC, HDL, hypertension, diabetes.

**Stop smoking! D:A:D**

Myocardial infarction relative risk ratios

![Graph showing incidence rate ratios for myocardial infarction](image)

**Petoumenos et al. HIV Medicine 2011**

**Age-adjusted rates of osteoporotic fractures in HIV patients**

![Graph showing age-adjusted fracture rates](image)

**Bozette et al. 2011**
Age is an important factor for osteoporotic fractures

![Graph showing age-related fracture risk](image)

Kanis JA et al Osteoporosis Int 2002;13:527-536

Multi-morbidity and frailty

Concept of **multi-morbidity**:  
- Total is greater than sum of parts

**Frailty phenotype**:  
- 3 of 5 (weight loss, exhaustion, weakness, slowness, and low physical activity)  
- associated with higher mortality in HIV
Frailty increases with age and time with HIV

9-fold higher risk than age-matched controls


Cancer-attributable mortality in HIV-patients on ART (North America, 1995-2009)

10% of death attributable to cancer in patients on ART

What’s killing the D:A:D cohort?

D:A:D cohort (49,731 PLWH)

Cause of death 1999–2000
- 91%
- 9% NADM
- Other causes

17.5 deaths per 1,000 PY

Cause of death 2009–2011
- 77%
- 23% NADM
- Other causes

9.1 deaths per 1,000 PY

Worm SW. BMC Infect Dis 2013;13:471

„Job description“ of HIV physicians

- Behavioural risk modification
- HIV therapy monitoring
- Toxicity management
- Screening/treatment of co-morbidities
- DDI management
- Psychosocial support
- Vaccination
- Partner counseling
- STI prevention/treatment PrEP
- HIV specialist
Co-morbidities in HIV patients: Hit hard, hit early????

- **Co-morbidities** are increasingly important in HIV medicine: (For physicians, patients, health care system, …)
- Which co-morbidities are **most relevant**?
- **Guidelines** (EACS) aim to help
- **Individualized therapy** more important for co-morbidity treatment, less for ART?
- **Interventional trials**: clinical endpoints / patient-reported outcomes / different regions of the world
**Summary**

**ART**
- Early diagnosis & treatment
- Contemporary ART
- Stop viral replication
- Prevent resistance mutations

**ART+**
- Co-morbidities
  - Screen
  - Treat
  - Prevent
  - Long term health

**ART+**
- Co-morbidities
  - Stop smoking
  - Reduce weight
  - Exercise
  - Long term health & Quality of life

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**Outlook**

<table>
<thead>
<tr>
<th>Diagnosed</th>
<th>On ART</th>
<th>&lt;50 copies</th>
<th>Good health</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
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