An Italian patient
Patient concerns

Will I grow old prematurely?

Will I dement?

Will I get heart disease?
Causes of death among Danish HIV patients compared to population controls in the period 1995-2008

Helleberg et al., Infection 2012
Complex issue

1. Accelerate ageing process
2. One of the factors making co-morbidity worse
3. ARV
   - better
   - worse
   - detectable
   - undetectable
Issues

- Clinical significance
- Cohorts
- Controls
- causatiom
Clinical v statistical significance

<table>
<thead>
<tr>
<th>Condition</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina + Aspirin</td>
<td>95%</td>
</tr>
<tr>
<td>Angina no Aspirin</td>
<td>93%</td>
</tr>
</tbody>
</table>

Would you take Aspirin?
Cohort studies

1. Channelling biases
2. Missing events
3. Lead / lag time
4. Closed/open
Observations in Cohort studies vs. RCTs
Beta-carotene intake and cardiovascular mortality

Cohorts

- Male health workers, USA
- Social insurance, men, Finland
- Social insurance, women, Finland
- Male chemical workers, Switzerland
- Hyperlipidaemic men, USA
- Nursing home residents, USA

Trials

- Male smokers, Finland
- Skin cancer patients, USA
- (Ex)-smokers, asbestos workers, USA
- Male physicians, USA

Relative risk (95% CI)

Egger et al. BMJ 1998
Antiretroviral Therapy, HIV RNA Suppression, and CD4+ Count.

NA-ACCORD study:
Higher mortality when deferring treatment

Kaplan-Meier survival estimates
NA-ACCORD study: Higher mortality when deferring treatment
Kitahata M et al. CROI 2009. Abstract 71

CD4 count >500 cells/mm³ & defer HAART (n=6,539)

CD4 count >500 cells/mm³ & initiate HAART (n=2,616)
CAUSATION ≠ ASSOCIATION
Is LPS Causing Immune Activation In Vivo?

- LPS-stimulated monocytes secrete sCD14 and shed surface CD14

![Graph showing plasma sCD14 levels in different groups.](image)

- Raised plasma sCD14 indicates chronic in vivo stimulation of monocyte/macrophages by LPS
Causation

degree of correlation

effects of eradication

Biological plausibility
Problems of Controls

- Hiv patients
- risk takers
- Impoverished
- Infected with many things

- Controls
- “nice” lab technicians
Controls in Iprex study

- 12% of the population at risk were osteopaenic before study start.
Mothers of control subjects
IRR = 1.31 95% CI: 1.08 – 1.60

Mothers of HIV patients

Rasmussen et al., BMC Infectious Diseases, 2011
If you want the Nobel Prize
If you want grant money

Mention HIV cure

Mention \( \uparrow \) co-morbidities as an accomplished fact
Diseases

- Cardiovascular
- Cancer
- Dementia
When did it all Start?  
Non-HIV outcomes – SMART Trial

- Risk of serious non-AIDS events in subset of patients in SMART trial
- 477 patients were ART-naïve or had been off ART for ≥6 months

<table>
<thead>
<tr>
<th>Number of events</th>
<th>Hazard ratio: deferred vs immediate ART (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART</td>
<td>Immediate ART</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>7.02 (1.57-31.4)</td>
</tr>
</tbody>
</table>

Adapted from The SMART Study Group. *J Infect Dis* 2008;197:1133-44.
Risk of CVD with ART Interruptions

<table>
<thead>
<tr>
<th>Event</th>
<th>DC</th>
<th>VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CVD</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Non-fatal clinical MI</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Non-fatal silent MI</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Coronary artery disease requiring surgery for invasive procedure</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>All major CVD events</td>
<td>48</td>
<td>31</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Years from Randomization</th>
<th>DC</th>
<th>VS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2752</td>
<td>2720</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>1306</td>
<td>1292</td>
</tr>
<tr>
<td>1.5</td>
<td></td>
<td>713</td>
<td>696</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>379</td>
<td>377</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

**SMART: Inflammatory markers associated with mortality**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>All-cause mortality</th>
<th>Unadjusted OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td></td>
<td>2.0 (1.0–4.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td>8.3 (3.3–20.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D-dimer</td>
<td></td>
<td>12.4 (4.2–37.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- 85 cases and 170 matched controls
- OR compared top quartile with bottom quartile

OR=odds ratio; DC=drug conservation

Alteration in immune activation after ART

[Graph showing changes in MFI log (CD38 on CD8+ T cells) over weeks on therapy, with a decrease observed from baseline to week 48. The normal range is shaded.]
Valgancyclovir Decreases CD8 Activation Significantly More Than Placebo

-4.4%

*P=0.033  *P=0.016

*P for difference in the change from week 0 between valgan- and placebo-treated groups.

Hunt CROI 2010
Risk of MI in patients presenting at least twice to either of two hospitals in Boston (1996–2004) according to HIV status

* Adjusted for age, gender, race, hypertension, diabetes and dyslipidaemia. Proportion of patients with hypertension, diabetes and dyslipidaemia significantly higher in HIV-positive vs HIV-negative cohort.
PIs/NNRTIs and Risk of MI: Cumulative Exposure to Each Drug

Lundgren JD, et al
Oral Abstract 44LB

* Approximate test for heterogeneity: \( P=0.02 \)
Increased cardiovascular relative risk observed with exposure to various risk factors:

- Protease inhibitors: RR/Year = 1.0
- Increasing age: RR/Year = 5.0
- Male gender: RR/Year = 4.0
- Current smoking: RR/Year = 0.9
- History of CV disease: RR/Year = 3.0
Potential clinical benefits for smoking cessation in HIV patients

- >27,500 HIV-positive patients in the D:A:D study
- Rates of CVD before and after smoking cessation

**Myocardial Infarction**

- Never smoked: 1.73
- Baseline status: 3.40
- Current: 3.73
- 1-2 yrs: 3.00
- 2-3 yrs: 2.62
- 3+ yrs: 2.07

**Cardiovascular disease**

- Never smoked: 1.28
- Baseline status: 2.19
- Current: 2.32
- 1-2 yrs: 1.84
- 2-3 yrs: 1.60
- 3+ yrs: 1.40

**Coronary heart disease**

- Never smoked: 1.60
- Baseline status: 2.48
- Current: 2.63
- 1-2 yrs: 2.48
- 2-3 yrs: 1.90
- 3+ yrs: 1.83

**Mortality**

- Never smoked: 0.99
- Baseline status: 1.28
- Current: 1.67
- 1-2 yrs: 1.02
- 2-3 yrs: 1.34
- 3+ yrs: 1.30

*Adjusted for age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes, and time-updated lipids and blood pressure assessments.*
Overall and age-specific incidence rates (IRs) (and 95% confidence intervals [CIs]) for myocardial infarction (MI) (A), end-stage renal disease (ESRD) (B), non-AIDS-defining cancers (including human immunodeficiency virus [HIV]-associated cancers) (C), and HIV-associated cancers (D), by HIV status, Veterans Aging Cohort Study Virtual Cohort April 2003–December 2010
VA cohort study

- Controls DID NOT get HIV
Age-adjusted rates of death

Cardiovascular Disease (CVD), Rates and Hazard Ratios by Year of Follow-up

Event Rates with 95% CI

- Immediate
- Deferred

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Rate/100 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>0.17 0.39</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.19 0.23</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.21 0.21</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.82 0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imm</td>
<td>2302</td>
</tr>
<tr>
<td>Def</td>
<td>2330</td>
</tr>
</tbody>
</table>

No. of Events:
- Imm: 4 4 3 7
- Def: 9 5 3 2

Imm/Def Hazard Ratio with 95% CI

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>0.45 (0.18)</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.80 (0.74)</td>
</tr>
<tr>
<td>Year 3</td>
<td>1.01 (0.99)</td>
</tr>
<tr>
<td>Year 4</td>
<td>3.32 (0.14)</td>
</tr>
</tbody>
</table>

Note: CI computed using exact poisson approximation.
Cardiovascular Disease (CVD), Rates and Hazard Ratios by Year of Follow-up

Event Rates with 95% CI

<table>
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<tr>
<th>Study Year</th>
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<th>Deferred</th>
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<td>0.39</td>
</tr>
<tr>
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<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
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<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
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<td>0.18</td>
</tr>
</tbody>
</table>

Imm/Def Hazard Ratio with 95% CI

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Hazard Ratio</th>
<th>P-value (unadj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>0.45</td>
<td>0.18</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.80</td>
<td>0.74</td>
</tr>
<tr>
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<td>0.99</td>
</tr>
<tr>
<td>Year 4</td>
<td>3.32</td>
<td>0.14</td>
</tr>
</tbody>
</table>

No. of Events:
- Imm: 4 4 3 7
- Def: 9 5 3 2

Person Years:
- Imm: 2302 2121 1424 1129
- Def: 2300 2130 1438 1124

Note: CI computed using exact poisson approximation.
Change in Metabolic Measures (Mean ± 2 SE)

**Total Cholesterol**

- **Months from randomization**
- **Change in total cholesterol from baseline (mg/dL)**
- **Imm.** vs **Def.**

**Low Density Lipoprotein (LDL)**

- **Months from randomization**
- **Change in LDL from baseline (mg/dL)**

**High Density Lipoprotein (HDL)**

- **Months from randomization**
- **Change in HDL from baseline (mg/dL)**

**Total Cholesterol/HDL**

- **Months from randomization**
- **Change in Total Cholesterol/HDL from baseline**

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**No. of participants:**

- **Total Cholesterol/HDLC**
- **Low Density Lipoprotein (LDL)**
- **High Density Lipoprotein (HDL)**

**P-values, t-tests, unadj.**

- <0.001 <0.001 <0.001 <0.001 <0.001

**Longitudinal mixed model, adj. for baseline and visit:**

- Est. diff.: 11.4 95% CI: 10.0 – 12.9 P-value: <0.001

---

**No. of participants:**

- **Total Cholesterol/HDLC**
- **Low Density Lipoprotein (LDL)**
- **High Density Lipoprotein (HDL)**

**P-values, t-tests, unadj.**

- <0.001 <0.001 <0.001 <0.001 <0.001

**Longitudinal mixed model, adj. for baseline and visit:**

- Est. diff.: 5.5 95% CI: 4.2 – 6.8 P-value: <0.001
Overall and age-specific incidence rates (IRs) (and 95% confidence intervals [CIs]) for myocardial infarction (MI) (A), end-stage renal disease (ESRD) (B), non-AIDS-defining cancers (including human immunodeficiency virus [HIV]-associated cancers) (C), and HIV-associated cancers (D), by HIV status, Veterans Aging Cohort Study Virtual Cohort April 2003–December 2010
Cancer in the AIDS population

Follow-up time at risk for cancer in both the AIDS and general populations, by age, for regions covered by the HIV/AIDS Cancer Match Study (1996 to 2007).

Points represent cases of cancer observed among persons with AIDS.
Cancer and oncogenic viruses

Increase risk of acquisition of HH8 HPV EBV
Cancers attributable to infections: declining relative relevance with age

Martel et al, AIDS 2015
### Types of Cancer

<table>
<thead>
<tr>
<th>Cancer event</th>
<th>Imm. ART</th>
<th>Def. ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Lymphoma, NHL + HL</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cervical or testis cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other types*</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>14</strong></td>
<td><strong>39</strong></td>
</tr>
</tbody>
</table>

**Immediate ART:** squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma.

**Deferred ART:** gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

**HR (Imm/Def):** 0.36  
(95%CI: 0.19 to 0.66,  
p=0.001)

*INSIGHT / START: Lundgren et al, NEJM 2015*
CHARTER study: high prevalence of neurocognitive impairment

CHARTER Study data: 2003–2007

Heaton et al, CROI 2009
Damaged brain may heal poorly
CD4 Nadir

- Legacy of prior damage
- Nadir CD4 count
  - CHARTER analysis suggest significant impact of nadir <350
  - Data too limited to test higher nadirs
- Implies earlier rx could be helpful
Background

Rates of neurocognitive impairment

Trends in HIV RNA (UK CHIC)
Incidence and impact on mortality of severe neuro-cognitive disorders in persons with and without HIV: a Danish nationwide cohort study

Figure 1: Incidence rates (IR) (per 1000 PYR, 95% confidence intervals) for severe neuro-cognitive disorders in HIV-infected patients (filled circles) and population controls (squares) by time periods; 1997-2000, 2001-2004 and 2005-2008.

François-Xavier Lescure et al. CID, 2011
Prospective study

200 patients
→
59 mood disorder GAD > 7
   PHQ > 15
→
124 normal 2 score
→
20 abnormal → Found testing 1 abnormal
Figure 1.
Change in overall speed and executive function domains over study period. (a) Change in composite speed domains from baseline [z-score changes; bars, 95% confidence interval (CI)]. (b) Overall changes in global neurocognitive score from baseline [z-score changes; bars, 95% CI]. (c) Change in executive function from baseline (number of errors; bars, 95% CI).
Age at estimated HIV seroconversion in CASCADE
Over 50’s clinic

- A weekly clinic was implemented, dedicated to all patients aged 50 years or above
- Patients were referred by their regular HIV out-patient clinicians
- The inter-disciplinary team consists of a consultant, specialist registrar and nurse practitioner, and all have their own appointment slots
- In addition the clinic is supported by a specialist pharmacist and all patients are discussed in a pre-clinic meeting
Activities

1. BMD (3 yearly)
2. CT heart (5 years)
3. Anal smear (self administered)
4. Adherence check
5. ‘Healthy living advice’
6. Smoking cessation (Vap)
7. Direct questioning about side effects
**Functional tests**

- Pulse Wave Velocity (PWV)*
- Flow Mediated Dilation (FMD)

**Structural tests**

- Intima Media Thickness (IMT)*
- Coronary calcium Score (CAC)*

* Independent from traditional cardiovascular risk factors