The purpose

- What are some of the comorbidities

- MORE IMPORTANTLY ARE THEY REALLY RELATED TO HIV AT ALL
The answer

• Comorbidities exist need to be handled

• BUT relationship with HIV enormous implications for when and how to treat
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
Non-Aids cancers

Diabetes mellitus

Chronic liver disease

CVD

Osteoporosis

Depression

Frailty

Cognitive disorders

Chronic renal disease

Images courtesy of Peter Reiss.
CAUSATION ≠ ASSOCIATION
Is LPS Causing Immune Activation In Vivo?

- LPS-stimulated monocytes secrete sCD14 and shed surface CD14

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

? degree of correlation

? effects of eradication

Biological plausibility
Cohort Studies

- How to make a silk purse out of a sow’s ear

Many hidden biases
Cohort studies

1. Channelling biases
2. Missing events
3. Lead/lag time
CHARTER study: high prevalence of neurocognitive impairment

CHARTER Study data: 2003–2007

Heaton et al, CROI 2009
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.
Our hand study

- Cross section on art frequency of “hand” same as general
- Population driven by anxiety

- Longitudinal on art tendency to improve
Anal Cancer

Relative risk of seminoma and nonseminoma in HIV

Head and neck cancer

Incidence of HIV related lung cancer compared to HIV negatives

Other studies have found a 2 fold increase (95%CI: 1.62-2.52) JCO '03
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.
Causes of death among Danish HIV patients compared to population controls in the period 1995-2008

Helleberg et al., Infection 2012
Mothers of control subjects

Mothers of HIV patients

IRR=1.31 95%CI: 1.08 – 1.60

Rasmussen et. al, BMC Infectious Diseases, 2011
Proper controls

- HIV indigent risk takers drug alcohol users

- Controls @ high risk of hiv but negative
BMD in Iprex

• 2045 individuals baseline DEXA

• Z score > -2 in 12%

• In San Fran osteoporosis 4.5% poppers
Life expectancy at birth (men)

Do they die of premature ageing in Glasgow or is it something different?

Which group of “normal Population would you choose to compare with your HIV population

<table>
<thead>
<tr>
<th>Location</th>
<th>Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow (deprived area)</td>
<td>54</td>
</tr>
<tr>
<td>Australian Indigenous</td>
<td>59</td>
</tr>
<tr>
<td>India</td>
<td>61</td>
</tr>
<tr>
<td>Philippines</td>
<td>65</td>
</tr>
<tr>
<td>Lithuania</td>
<td>66</td>
</tr>
<tr>
<td>US</td>
<td>75</td>
</tr>
<tr>
<td>UK</td>
<td>76</td>
</tr>
<tr>
<td>Australian average</td>
<td>77</td>
</tr>
<tr>
<td>Glasgow (affluent area)</td>
<td>82</td>
</tr>
</tbody>
</table>

Untangling HIV from comorbidities
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>7.02 (1.57-31.4)</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from The SMART Study Group. *J Infect Dis* 2008;197:1133-44.
Untangling HIV comorbidities

• The consequences of:
  – HIV viraemia
  – Immunodeficiency
  – Inflammation
  – HAART
Now what about the Incidence ratios for non-AIDS events

*Also adjusted for peak viral load, age, HIV exposure group, region of Europe, hepatitis B and C status, diabetes, hypertension, smoking status, on cART, prior AIDS and CD4 count

Untangling HIV comorbidities

CD4 count

- HIV comorbidities

What is the association with

- current CD4 count
Serious non-AIDS events and latest CD4 (adjusted hazard ratio /100 cells/mm$^3$ higher)

(i) Liver disease / death

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of events</th>
<th>Includes non-fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>DAD</td>
<td>301</td>
<td>No</td>
</tr>
<tr>
<td>CASCADE</td>
<td>46</td>
<td>No</td>
</tr>
<tr>
<td>SMART</td>
<td>25</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(ii) Non-AIDS cancer / death

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of events</th>
<th>Includes non-fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>32</td>
<td>Yes</td>
</tr>
<tr>
<td>DAD</td>
<td>255</td>
<td>No</td>
</tr>
<tr>
<td>CASCADE</td>
<td>46</td>
<td>No</td>
</tr>
<tr>
<td>SMART</td>
<td>49</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(iii) Renal disease / death

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of events</th>
<th>Includes non-fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>DAD</td>
<td>27</td>
<td>No</td>
</tr>
<tr>
<td>SMART</td>
<td>18</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(iv) Cardiovascular disease / death

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of events</th>
<th>Includes non-fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>24</td>
<td>Yes</td>
</tr>
<tr>
<td>DAD</td>
<td>855</td>
<td>Yes</td>
</tr>
<tr>
<td>CASCADE</td>
<td>36</td>
<td>No</td>
</tr>
<tr>
<td>SMART</td>
<td>145</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adapted from Phillips AN. *AIDS* 2008;22:2409-18
### Association Between Current CD4+ Cell Count and Non-AIDS Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-AIDS Cancer/Death</th>
<th>Renal Disease/Death</th>
<th>CVD Events/Death</th>
<th>Liver Disease/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>Yes</td>
<td>Yes</td>
<td>Trend</td>
<td>No</td>
</tr>
<tr>
<td>D:A:D</td>
<td>Yes</td>
<td>Yes</td>
<td>Trend</td>
<td>Yes</td>
</tr>
<tr>
<td>CASCADE</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SMART</td>
<td>Trend</td>
<td>Trend</td>
<td>Trend</td>
<td>Yes</td>
</tr>
</tbody>
</table>

But is there a threshold for these events? Impact of cART on non-AIDS events – Johns Hopkins HIV Clinical Cohort

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Events/pyrs</th>
<th>Non-infectious comorbidity(/100 pyrs)</th>
<th>IRR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td></td>
<td>0.53 (0.42-0.67)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>HAART</td>
<td>125/1029</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HAART</td>
<td>400/1495</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>201-350</td>
<td></td>
<td>0.5 (0.41-0.81)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>HAART</td>
<td>64/1022</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HAART</td>
<td>151/1172</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td></td>
<td>0.78 (0.52-1.15)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>HAART</td>
<td>103/2023</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HAART</td>
<td>185/2386</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Moore RD. Clin Infect Dis 2008;47:1102-4
# CD4 nadir and NADM – D:A:D Study

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latest CD4 count</td>
<td>0.97</td>
<td>0.95, 0.98</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nadir CD4 count &lt;100 cells/mm³</td>
<td>1.22</td>
<td>1.03, 1.44</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration of immunosuppression (&lt;200) Per year</td>
<td>1.04</td>
<td>1.02, 1.05</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Worm S. Abstract 130, 19th CROI, March 5-8, 2012, Seattle.
CD4 nadir and neurocognitive impairment

- 1525 HIV+ve patients,
- CD4 nadir: 172 (48, 297) cells/ml, current CD4 count: 420 (262, 603) cells/mm³
- Nadir CD4 count determined by self-report
- CHARTER analysis suggest significant impact of nadir <350
  - Data too limited to test higher nadirs

CROI 2010, Poster 429, Ellis, et al
Other Mechanisms of Non–AIDS comorbidities

Inflammation
Alteration in immune activation after ART
Valgancyclovir Decreases CD8 Activation Significantly More Than Placebo

-4.4%

*P=0.033  *P=0.016

% CD38+ HLA-DR+ CD8+T Cells

Week of Therapy

On Study Drug  Off Drug

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

Hunt CROI 2010
## SMART: Inflammatory markers associated with mortality

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

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

OR=odds ratio; DC=drug conservation

### JUPITER Baseline Blood Levels (median, interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (N = 8901)</th>
<th>Placebo (n = 8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>hsCRP, mg/L</strong></td>
<td>4.2 (2.8 - 7.1)</td>
<td>4.3 (2.8 - 7.2)</td>
</tr>
<tr>
<td><strong>LDL, mg/dL</strong></td>
<td>108 (94 - 119)</td>
<td>108 (94 - 119)</td>
</tr>
<tr>
<td><strong>HDL, mg/dL</strong></td>
<td>49 (40 – 60)</td>
<td>49 (40 – 60)</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/L</strong></td>
<td>118 (85 - 169)</td>
<td>118 (86 - 169)</td>
</tr>
<tr>
<td><strong>Total Cholesterol, mg/dL</strong></td>
<td>186 (168 - 200)</td>
<td>185 (169 - 199)</td>
</tr>
<tr>
<td><strong>Glucose, mg/dL</strong></td>
<td>94 (87 – 102)</td>
<td>94 (88 – 102)</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>5.7 (5.4 – 5.9)</td>
<td>5.7 (5.5 – 5.9)</td>
</tr>
</tbody>
</table>

All values are median (interquartile range). [ Mean LDL = 104 mg/dL ]
So does treatment improve things? ACTG 5224s Biomarker Results: hsCRP and IL-6

Conclusion: Small differences between the ARVs studied are unlikely to be of clinical significance. hsCRP=high-sensitivity C-reactive protein; IL-6=interleukin-6

But are we missing subclinical disease?

Coronary Artery Calcium

No Calcification

Severe Calcification

LAD

PA

Aorta

Left Main

Left Main

LA

LCX
MACS: Subclinical atherosclerosis
Cross sectional analysis results

- Similar prevalence of CAC among HIV+ and HIV- men, after adjusting for CVD risk factors
- Among men with CAC, the extent of CAC is lower in HAART treated men than HIV- men
- Carotid IMT and plaque do not differ between HIV+ and HIV- men

So you are still convinced of the association Co morbidities and HIV- What the studies show

- **CVD**
  - Million patient study AMI increased in HIV + RR 1.75(1.5-2.0)
  - *Triant 2007*

- **Bone**
  - Increase in fracture risk HIV + vs HIV- matched age ethnicity geography
  - 2011

- **Brain**
  - In patients well controlled on HAART Asymptomatic NCI 19% -*Garvey 2011*

- **Cancer**
  - Anus, lung and Hodgkins are associated with HIV -*Shiels 2010*
• **CVD** different conclusions!
  – Million patient study AMI increased in HIV + RR 1.75(1.5-2.0)
  – **Not controlled for smoking, coinfection, comorbidities and recreational drugs and other behaviours** - *Trian* 2007

• **Bone**
  – Increase in fracture risk HIV + vs HIV- matched age ethnicity geography
  – But once other fracture risk factors and BMI included in analysis the risk disappeared - *Womack* 2011

• **Brain**
  – In patients well controlled on HAART Asymptomatic NCI 19% comparable to normal population - *Garvey* 2011

• **Cancer**
  – Once account for age distributions bias compared with population only anus lung and Hodgkins are associated with HIV all have been linked to smoking or viral
But look at Traditional CVD risk factors

Significantly higher proportions of hypertension, diabetes and dyslipidaemia in HIV-positive vs HIV-negative patients (p<0.0001 for all)

CVD=cardiovascular disease; ICD=international classification of disease

What is ageing?

Ageing is the accumulation of inflammatory events that eventually result in organ failure and death.

Increase in biomarkers:

- Interleukin-6
- TNF-α
- β2-microglobulin
- C-reactive protein
- Erythrocyte sedimentation rate
- TH1 lymphocyte%
- etc.
## Age, HIV and the immune system

<table>
<thead>
<tr>
<th>HIV</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 lymphopaenia</td>
<td>CD4 lymphopaenia</td>
</tr>
<tr>
<td>Inverted CD4:CD8 ratio</td>
<td>Inverted CD4:CD8 ratio</td>
</tr>
<tr>
<td>Reduced thymic output</td>
<td>Reduced thymic output</td>
</tr>
<tr>
<td>Reduced naïve cells</td>
<td>Reduced naïve cells</td>
</tr>
<tr>
<td>Shorter telomeres of CD8</td>
<td>Shorter telomeres of CD8</td>
</tr>
<tr>
<td>cells</td>
<td>cells</td>
</tr>
</tbody>
</table>
Ageing and HIV –is it premature?

The problem is the choice of control group who are compared to the HIV positive group.

HIV positive persons are not usually comparable to a normal population as they have one or more factors that confound comparisons, e.g.

- More smoking
- More recreational drugs
- More infectious diseases
- They are from poorer economic strata
- More psychological problems etc
Conclusions

Co morbidities, Ageing and HIV

Co morbidities will increase as the HIV population ages.

Need good studies that can cut the Gordian Knot of cause and effect.

While we are busy measuring, we should be busy intervening where we can!!
Conclusions

Reassure patients: primarily a lifestyle issue - treatment

Caveat: may need to treat before irreversible changes
Age

Death be not proud though some have called thee mighty and dreadful for thou art not so.

John Donne (1631)