HIV and the CARDIOVASCULAR SYSTEM

Dr Dave Spencer  Right to Care The Helen Joseph Hospital Johannesburg and the SA HIV Clinicians’ Society
Our Vision
That every individual has ready access to quality medical services that prevent, treat, and manage HIV infection and associated diseases.

Our Mission
To deliver and support quality clinical services, in Southern Africa, for the prevention, treatment, and management of HIV and associated diseases.
## Mortality rates: deaths per 1000 person years (95% CI)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>16.3 (14.9-17.8)</td>
<td>12.4 (11.5-13.2)</td>
<td>10.0 (9.3-10.8)</td>
<td>12.0 (11.5-12.5)</td>
</tr>
<tr>
<td>Between ages 20-44yr</td>
<td>13.1 (11.7-14.7)</td>
<td>10.3 (9.4-11.2)</td>
<td>7.5 (6.8-8.3)</td>
<td>9.7 (9.1-10.2)</td>
</tr>
</tbody>
</table>

## Potential years of life lost before age 65 years per 1000 person years

| 20-64 years | 365.9 | 260.4 | 189.4 | 247.0 |

## Life-expectancy in adjusted years

| At exact age 20 years | 36.1 (SE 0.60) | 41.2 (SE 0.52) | 49.4 (SE 0.54) | 43.1 (SE 0.33) |
| At exact age 35 years | 25.0 (SE 0.42) | 30.1 (SE 0.31) | 37.3 (SE 0.37) | 31.7 (SE 0.21) |
| % surviving from 20-44 yr | 75.5% | 79.5% | 85.7% | 81.1% |

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A person starting combination ART at 20 years of age can expect to live about 43 years - about 2/3rds as long as the general population in rich income countries.

Data: 14 cohort studies  n = 43,355 HIV+ve patients over 10 years

Life-expectancy differs for different patient groups: injecting drug users and those starting ART at low CD4 levels are at greater risk

AIDS and Non-AIDS-related deaths have significantly decreased over time. But deaths still occur.

The Rate of Non-AIDS deaths by Calendar time in the EuroSIDA Study.

Test for Trend: p<0.0001

Why should HAART reduce the incidence of non-AIDS related deaths?

EuroSIDA 2005

In Europe AIDS only caused 36% of deaths in 2005 in HIV+ve persons

- Non-AIDS infections 5%
- Non-AIDS cancers 16%
- Liver disease 15%
- Cardiovascular disease 9%
- Suicide 5%
CHD Risk by Most Recent CD4+ Count*

HIV Positive on ART
- CD4+ ≥ 500
- CD4+ 201-499
- CD4+ ≤ 200

HIV Positive Not on ART
- CD4+ ≥ 500
- CD4+ 201-499
- CD4+ ≤ 200

Rate Ratio (95% CI)

<table>
<thead>
<tr>
<th>Reference</th>
<th>CD4+ Count</th>
<th>Rate Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Negative</td>
<td>CD4+ ≥ 500</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4+ 201-499</td>
<td>1.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>CD4+ ≤ 200</td>
<td>1.7</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HIV Positive</td>
<td>CD4+ ≥ 500</td>
<td>1.3</td>
<td>.19</td>
</tr>
<tr>
<td>Not on ART</td>
<td>CD4+ 201-499</td>
<td>1.1</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>CD4+ ≤ 200</td>
<td>1.5</td>
<td>.29</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, sex, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid-lowering and antihypertensive therapy. The following factors were time varying in the analysis: ART, CD4+ cell count, age, diabetes, lipid-lowering therapy, antihypertensive therapy, remaining factors were fixed variables.

Figure. CD4 cell count and Coronary Heart Disease Risk in HIV-infected Patients
Why does infection with the human immunodeficiency Virus cause death?
Why does HIV infection cause death?
With the introduction of HAART, the proportion of deaths due to infectious causes in HIV/AIDS patients has declined from 80% to 43.6%, and a higher proportion of deaths has been attributed to non-infectious causes, with cardiovascular disease (CVD) causing 21.8% of deaths in the HAART era compared with 8.4% in the pre-HAART era.


CARDIOVASCULAR DISEASE IN HIV-INFECTED PATIENTS
HIV infection leads to premature ageing: conditions associated with older age occur a decade or more earlier.
WHY DOES AIDS OCCUR?

- loss of immune cells (CD4+)
- PERSISTENT IMMUNE ACTIVATION
- persistent viral replication and activity

Causes of Immune activation

- HIV-1 infection and replication
- Massive CD4+ T cell depletion
- Bacterial translocation
- Production of HIV proteins Gp120, nef
- Viral reactivation
- Bacterial translocation

Systemic immune activation
Adaptive and Innate

Anti-HIV Immune response
Ag stimulation: HIV & other

M. Erasmus 2011
IMMUNE ACTIVATION IN HIV:

BACTERIAL TRANSLOCATION AND THAT OF THE PRODUCTS OF BACTERIAL BREAKDOWN [BACTERIAL DEBRIS]
The afferent arm of the GIT immune system incorporates specialized surface epithelial tissue including the microfold or M cells.

Below these cells and in close proximity to them, are discrete lymphoid follicles buried in the intestinal sub-mucosa.

This system permits the recognition and trapping of antigen and its subsequent processing.

Whole mount preparation demonstrating a lymphoid follicle in the lamina propria and sub-mucosa of the colon.
EM of the passage of HIV-virions across the intestinal epithelial border to the submucosal surface.

Virus may be transported through the epithelial cell or between epithelial cells or through the M cell...

Figure: Rabbit ileum containing Peyer’s patches and M cells.
Microbial translocation from the “leaky GUT” seems to be driving the chronic immune activation that is a hallmark of HIV infection.

Figure. Correlation of plasma levels of bacterial 16S ribosomal DNA (rDNA) with plasma levels of lipopolysaccharide (LPS) among ART-treated patients with low or undetectable HIV viremia.

Figure. Correlation of pretreatment plasma levels of bacterial 16S ribosomal DNA (rDNA) with indices of immune activation.
A. In treatment-naïve subjects, correlation of plasma levels of bacterial 16S rDNA with frequencies of CD38+HLA-DR+CD8+T cells (n=54)
B. At the end of 48 weeks of ART, inverse correlation of plasma levels of bacterial 16S rDNA with the magnitude of increases in CD4 T cell counts. (n=20)

ANTIRETROVIRAL THERAPY DRIVES DOWN PLASMA LEVELS OF LPS

*J Infect Dis* 2009; 199: 1177-1185
The increased risk of cardiovascular disease: why?

- chronic inflammation
- metabolic effects of the ARVs
- accelerated atherogenesis
As the neutrophil rolls along the vessel wall, the L-selectin adhesion molecule on its surface binds to the carbohydrate structures (Sialyl-Lewis bodies) on corresponding adhesion molecules on the vascular endothelium.

An increased risk of cardiovascular disease has been associated with elevated circulating levels of adhesion molecules released from vascular endothelium: **Soluble intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1)**

**TYPE-2 SOLUBLE RECEPTOR FOR TNF-α (sTNFR2)** = a marker of inflammation

Serum concentrations of sTNFR2 were significantly higher (p.001) in HIV-positive subjects than in controls. Similarly serum concentrations of ICAM-1 and VCAM-1 were elevated in this group.

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<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean ± SEM</th>
<th>Mean ± SEM</th>
<th>Mean ± SEM</th>
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</thead>
<tbody>
<tr>
<td>HIV-seronegative</td>
<td></td>
<td></td>
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<tr>
<td>subjects (n = 31)</td>
<td></td>
<td></td>
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<tr>
<td>sTNFR2 (ng/mL)</td>
<td>2.88 ± 0.13</td>
<td>5.11 ± 0.36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>282 ± 12</td>
<td>424 ± 23</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VCAM-1 (ng/mL)</td>
<td>821 ± 73</td>
<td>1113 ± 71</td>
<td>.008</td>
</tr>
</tbody>
</table>

Plasma concentrations of type 2 soluble receptor for TNF-α (sTNFR2), soluble intercellular adhesion molecule-1 and vascular adhesion molecule-1 (VCAM-1).

The relationship of the soluble receptor type 2 for TNF-α (s-TNFR2) and the soluble intercellular adhesion molecule-1 (ICAM-1) in persons who are HIV infected (■) compared with uninfected (●) age and gender-matched controls.

N = 52 HIV +ve (■)

The graph demonstrates a direct relationship between the adhesion molecules (ICAM-1 and (VCAM-1) and the inflammatory marker, sTNFR2

N = 31 HIV -ve (●)

Melendez MM et al. Endothelial Adhesion Molecules Are Associated with Inflammation in Subjects with HIV Disease. CID 2008;46:775-80
CIRCULATING LEVELS OF ADHESION MOLECULES ARE POSSIBLY ASSOCIATED WITH INFLAMMATION

...and by implication, an increased risk of cardiovascular disease.

Dyslipidaemia and obesity are associated with the increased circulation of endothelial adhesion molecules (ICAM-1)

Reductions in ICAM-1 levels occur with weight reduction AND CALORIE RESTRICTION

Paton N, the Insight SMART Study Group. Association between activation of inflammatory and coagulation pathways and mortality during long-term follow up in SMART. 5th Conference on HIV Pathogenesis, Treatment and Prevention, IAS 2009; Cape Town, July 18-22. Abst MOPEA034

N=5472 SMART patients
ART-interruption Study.
Deaths: Early group, <2yr (n=95)  Late group, > 2 yr (n=71)
Controls: age, gender, HIV+ve

**IL-6 levels** were higher in both the early and late deaths
(OR early = 5.7, CI 2.6-12.6)
(OR late = 5.0, CI 2.0-12.9)
(P = .0007)

**D-dimer** levels were higher in both the early and late deaths:
(OR early = 5.7, 2.6-12.8)
(OR late = 4.9, 1.6-14.5)
( p = .0005)

HIV-infected patients with elevated D-dimers and IL-6 are at an increased risk of death. This association persists in long term follow up.
Substudy of a CD4-guided HAART Interruption Study

N = 54 patients with samples up to 36 months.
Controls: Therapy Continuation group vs Interruption group

Markers of inflammation increased in the group that interrupted therapy vs those who continued:

- MCP-1 (p = .026)
- sP-selectin (p = .020)
- sV-CAM (p = .035)
- sCD40L (trend towards increase)
- IL-6: trended lower in the TC (Therapy Continued) group, but not significant
- t-PA and IL-8: results not conclusive

HAART interruption appears to be associated with an increase in inflammatory cytokines/ markers. These cytokines correlate with endothelial damage and the development of atheromatous plaque.
Proposed Mechanisms for Accelerated Atherogenesis in HIV-infected Patients

INTERLEUKIN-18 (IL-18)

IL-18 accelerates atherogenesis in animal models

IL-18 is released from ischaemic cardiac muscle and suppressed contractility

IL-18 and its receptors are increased in atherosclerotic arteries

IL-18 is upregulated in adipocytes and participates in the development of the metabolic syndrome

IL-18 is released from platelet aggregates during the process of adhesion to atheromatous plaque

It is suggested that IL-18 may have a central role in the development of cardiovascular disease in HIV-infected patients.

This cytokine is up-regulated in HIV-infection. It participates in atherosclerosis and contributes to left-ventricular dysfunction.

Torre D, Pugliese A. Interleukin 18 and Cardiovascular Disease in HIV-1 Infection: A Partner in Crime? *AIDS Rev* 2010; 12: 31-9
What is the clinical expression of heart disease in those who are HIV infected?
In the pre-ART era, 8% of HIV-positive persons were found to have a dilated cardiomyopathy (CMO) in a large echocardiographic study of 952 asymptomatic subjects. CMO in this study was associated with:

- Low CD4 count
- Use of zidovudine
- Presence of a myocarditis


CARDIAC ABNORMALITIES IN HIV-POSITIVE CHILDREN

N=96 [65 on ART]
N=62 of 96 WHO 3 and 4
N=32 with cardiac abnormalities on Echo and/or ECG.
N=22 LVD [3=ART naive]
N=2 DCM
N=16 pericardial effusion [n=5 ART naive]

15 of 19 children with LVD were on ZDV and 4 on d4T. (p = .008)

Prospective, random sampling.

Kilimanjaro Christian Medical Center, Northern Tanzania
N=656 Cross-sectional Study
Age = 41yr (mean). [35-47yr]
Gender: 24% women
Ethnic background: 29% non-Hispanic Black, 10% Hispanic
Median CD4 = 462 [CD4 range 326-661]
73% currently on ART of whom 91% had vl.<400cp/ml
Duration known HIV+ve: 6yr
Median, range [2.3-8.1]

Co-infection with HBV = 21 (5%)
Co-infection with HCV = 84 (19%)
Diagnosis of hypertension = 199 (30%)
Diagnosis of pulmonary HTN = 3 (<1%)
Current smoker = 280 (44%)
Current drug use
Cocaine = 80 (13%)
Marijuana = 200 (31%)
BMI, median value = 25.5 [range 22.8-28.6]
Duration on ART = 2.3yr, median [0.6-5.0]

Baseline Characteristics of SUN Study Participants who Underwent Echocardiography


<table>
<thead>
<tr>
<th>Cardiac Abnormality: associations</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.V.Dysfunction: History of MI</td>
<td>15.9</td>
<td>1.94-3.29</td>
<td>.019</td>
</tr>
<tr>
<td>hsCRP level&gt;5µg/L</td>
<td>1.70</td>
<td>1.03-2.77</td>
<td>.033</td>
</tr>
<tr>
<td>Current tobacco smoking</td>
<td>1.57</td>
<td>1.03-2.34</td>
<td>.036</td>
</tr>
<tr>
<td>Diastolic Dys: hsCRP level&gt;5µg/L</td>
<td>1.61</td>
<td>1.05-2.46</td>
<td>.027</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.87</td>
<td>1.24-2.83</td>
<td>.003</td>
</tr>
<tr>
<td>Pulm HTN: Current use of ritonavir</td>
<td>1.75</td>
<td>1.04-3.00</td>
<td>.037</td>
</tr>
<tr>
<td>LV Hypertrophy: Hypertension</td>
<td>3.56</td>
<td>1.57-8.25</td>
<td>.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.51</td>
<td>1.60-12.1</td>
<td>.003</td>
</tr>
<tr>
<td>Black or Hispanic race</td>
<td>3.30</td>
<td>1.43-8.15</td>
<td>.006</td>
</tr>
<tr>
<td>Women with MBI&gt;25</td>
<td>3.40</td>
<td>1.43-8.05</td>
<td>.005</td>
</tr>
<tr>
<td>hsCRP level&gt;5µg/L</td>
<td>2.69</td>
<td>1.20-6.02</td>
<td>.015</td>
</tr>
<tr>
<td>Current use of abacavir</td>
<td>3.88</td>
<td>1.63-9.20</td>
<td>.002</td>
</tr>
<tr>
<td>LA Enlargement: Hypertension</td>
<td>1.66</td>
<td>1.14-2.41</td>
<td>.008</td>
</tr>
<tr>
<td>Marijuana use within past 6 months</td>
<td>1.56</td>
<td>1.10-2.22</td>
<td>.013</td>
</tr>
</tbody>
</table>

Predictors of Echocardiographic Abnormalities among SUN Study Participants
Many factors associated with echocardiographic abnormalities were traditional risk factors. We found that the duration on cART was NOT a factor in echocardiographic changes, though current use of a ritonavir-boosted PI and abacavir were independently associated with pulmonary hypertension and LV hypertrophy respectively.
Figure. FDA Meta-analysis of Risk of Myocardial Infarction in Abacavir Trials.
Protease inhibitors and cardiovascular outcomes: the HOPS data

Holmberg SD, Moorman AC. et al. Lancet 2002; 360:1747-48

Holmberg SD, Moorman AC, Greenberg AE. NEJM 2004;350:730-32

Figure 1. Rate of Myocardial Infarction (Panel A) and Percentages of Patients Taking Protease Inhibitors and Statins or Other Lipid-Lowering Therapy (LLT) (Panel B) in the HIV Outpatient Study, 1993 through 2002.

Rate of myocardial infarction over time in patients on PIs

3247 HIV +ve patients from outpatient clinics in 9 centers in the USA followed for 17,712 total person-years of observation

Protease inhibitor use

Statin or other lipid-lowering agent
The DATA COLLECTION on ADVERSE EVENTS of ANTI-HIV DRUGS = D:A:D STUDY

Prospective, observational study formed from 11 separate cohorts = 33,347 HIV-infected subjects at 212 clinics in Europe, Australia and the USA.

Duration: 2000-2007 (ongoing)
Risk of Myocardial Infarction According to Exposure to cART

The DAD Study: The Data Collection and Adverse Events Study
Observational Study of 11 separate cohorts of HIV+ve patients.

- 27% develop high TC (>6.2 mmol/l) on a PI-regimen of cART
- 23% develop high TC on a NNRTI-regimen
- 10% on a triple NRTI-regimen


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The proportion of patients at high risk of cardiovascular disease increased from 35.3% during 1999-2000 to 41.3% during 2005-2006.

Of the 28,985 patients 2801 (9.7%) initiated lipid-lowering therapy.

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9.7% started on lipid-lowering agents:
The rate of starting lipid-lowering agents was highest in

Men
Higher BMI
Positive Family History
Concurrent diabetes mellitus
Previous Cardiovascular event
Older age group
Changes in Incidence of Myocardial Infarction over Time in the DAD Study.

By February 2006, 455 episodes of MI had been reported over 137,310 PY follow-up. Median follow-up time 4.5yr. Event rate 0.32 episodes per 100PY (95% CI, 0.29-0.35)

During the follow-up period events were assessed in 6 calendar time periods viz. 1999-2000, 2001, 2002, 2003, 2004, 2005-2006. After adjustment for the baselines demographics and risk factor status at enrollment, there was a small and non-significant decrease in MI over time.
Cross-sectional study of carotid intima-medial thickness (cIMT) HIV+ve patients without pre-existing CVD or adjusting for risk factors vs HIV-ve age, gender matched controls (n = ?, not on ART)

Internal carotid mean intima-medial thickness =
HIV+ve  1.17 ± 0.50 mm
HIV-ve  1.06 ± 0.58 mm  ($p < .0001$)

HIV infection was accompanied by more extensive atherosclerosis measured by IMT. This was particularly obvious in the internal carotid and bulb region. The association of HIV infection with IMT is similar to that of traditional CVD risk factors (e.g. smoking)

CAROTID INTIMA MEDIA THICKNESS INCREASED IN HIV

Cross-sectional study of consecutive 92 HIV+ve clinic patients >40yr. Mean age 49.5 ± 7.4yr. Excluded IVDU.

Rest and post-exercise ankle-brachial index (ABI): measure blood pressure via doppler probe and sphygmomanometer: able to measure reduction in arterial luminal diameter.

Duplex scan of the arteries: define presence of plaque and luminal stenoses.

Background risk profile:

white (88%), male (76.1%), current smokers (62%), hypertension (27.2%) diabetic (4.3%), elevated TGLs (35.9%), low HDL-c (17.4%), metabolic syndrome (27.2%)
All patients (100%)

Patients with post-exercise (ankle-brachial index) ABI decrease >25% from resting (20.7%)

Asymptomatic patients with normal ABI (72.7%)

Patients with resting ABI <0.90 (9.8%)

Duplex scan revealed atherosclerotic plaques in iliac and femoral arteries of all these patients

Patients with claudication (15.2%)


Atherosclerotic plaques found in all patients tested (n =7)
Multivariate analysis identified age, smoking, diabetes, CD4+ <200c/µl are important and significant predictors of PAD.

Dyslipidaemia, metabolic syndrome and family history did not reach statistical significance...

The overall prevalence of PAD of 20.7% in this group is far higher than that of non-HIV infected populations.

The incidence of PAD in the general population ±1% at 50yr, 3% at 60yr.

Prevalence of PAD in male smokers aged 45-50yr who are HIV-ve, is ±1%.

Functional response of the brachial artery to

1. Flow-mediated dilatation: Blood pressure cuff occlusion of the artery x 5 minutes followed by release of the cuff – endothelium dependent

2. Nitric oxide dilatation: nitroglycerin 0.4mg sublingual i.e. non-endothelium dependent

Measured diameter of the brachial artery and flow velocity through the artery at rest and during dilatation

BRACHIAL ARTERY ULTRASOUND MEASUREMENTS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Flow-mediated dilatation (FMD) difference % (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Infection</td>
<td>3.6 (1.8-5.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.8 (0.2-3.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>4.2 (2.5-5.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Body Mass Index (BMI) &gt;30kg/m²</td>
<td>3.1 (1.2-4.9)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Multivariate analysis of risk factors for impaired endothelial function among 302 HIV+ve/HIV-ve matched subjects
<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>N = 75 HIV+ve subjects</th>
<th>N =32 subjects on PI’s</th>
<th>N = 43 subjects not on PI’s</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist diameter, mean cm ± SD</td>
<td>91 ± 16</td>
<td>96 ± 21</td>
<td>88 ± 11</td>
<td>.04</td>
</tr>
<tr>
<td>Waist-to-hip ratio, mean ± SD</td>
<td>0.9 ± 0.1</td>
<td>0.94 ± 0.1</td>
<td>0.88 ± 0.1</td>
<td>.01</td>
</tr>
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</table>

Patients on PI’s were more obese.

HIV-infected subjects had significantly lower Flow-Mediated Dilatation (FMD) compared with HIV-uninfected controls (7.3% ± 4.4% vs. 11.1% ± 6.3%, respectively)

Non-endothelium-dependent Nitroglycerine-Mediated Dilatation (NMD) did not differ between the two groups

i.e. HIV-infected subjects had significantly more endothelial dysfunction than controls

Coronary artery calcium (CAC) is a marker of the biological age of an individual. This may differ from their chronological age.

Cross-sectional observational study of 400 consecutive HIV-positive outpatients from Jan. 2006-June 2007. (Italy and Chicago, USA)

Patient characteristics:

- Age: 48yr (mean; range 20-76)
- BMI: 23.8 (mean, SD, 3.7)
- DM: 68 (17%)
- On lipid-lowering agents: 94 (23.5%)
Prevalence of coronary artery calcium (CAC) in the entire cohort and coronary age distribution in the subpopulation with a CAC score > 0.

All patients underwent cardiac computerized tomography (CT) scanning.

Images enabled the quantification of CAC. A CAC score was obtained.

This enabled vascular age to be determined using the CAC score and age, race and gender.

CONCLUSIONS:

We found evidence of aging in nearly half of our patients.

The 10-year risk of a cardiovascular event for a 50yr-old man with a CAC score of 56 is comparable to that of a 68yr old (95% CI, 67-70yr old), i.e. is 12%.

Increased coronary age was also predicted by higher CD4 cell count: ? Perhaps a marker of longer exposure to HAART though the authors argue that the CD4 level may be a marker of interferon-γ, a mediator of vascular inflammation and known to be atherogenic.
HIV ITSELF AND ITS TREATMENT IS ASSOCIATED WITH PROFOUND METABOLIC CHANGES THAT ALSO INFLUENCE LONG TERM SURVIVAL AND HEALTH OUTCOMES
Before the start of ART
ADVANCED HIV INFECTION

High TGLS
LOW TC
Low LDL-C
Low HDL-C

HAART:
High TGL, High TC, High LDL, Low HDL and IR
<table>
<thead>
<tr>
<th>NRTI/NtRTi analogues</th>
<th>Serum lipids</th>
<th>Serum glucose and insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine</td>
<td>Increase in total cholesterol (TC) and triglycerides (TGL)</td>
<td>Insulin resistance (IR), increased serum insulin</td>
</tr>
<tr>
<td>stavudine</td>
<td>Increase in TC and TGL</td>
<td>IR</td>
</tr>
<tr>
<td>didanosine</td>
<td>Increase in TC and TGL</td>
<td>IR</td>
</tr>
<tr>
<td>Tenofovir, abacavir, lamivudine, emtricitabine</td>
<td>No significant effect</td>
<td>No significant effect</td>
</tr>
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</table>

### METABOLIC SIDE-EFFECTS OF ART

<table>
<thead>
<tr>
<th>Non-nucleoside RTIs</th>
<th>Serum lipids</th>
<th>Serum glucose and insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Increase in TC, HDL and LDL cholesterols No effect on TGL</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Increase in HDL, no effect on other lipids</td>
<td>No significant effect</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Serum lipids</th>
<th>Serum glucose and insulin</th>
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</thead>
<tbody>
<tr>
<td>Atazanazir</td>
<td>No significant effect</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Increase in TC and HDL and TGL</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Increase in TC and TGL</td>
<td>IR (insulin resistance)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Aluvia/Kaletra)</td>
<td>Increase in TC and TGL</td>
<td>IR</td>
</tr>
<tr>
<td>Ritonavir full dose</td>
<td>Increase in TC and TGL</td>
<td>IR</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>No significant effect</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Increase in TC and TGL</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Protease inhibitors and glucose metabolism

Indinavir
Ritonavir
Amprenavir

- Inhibit glucose uptake in adipocytes via the selective inhibition of the glucose transport protein, Glut 4

Indinavir
Ritonavir

- Impair the activation of sterol regulatory binding protein 1 (SREBP-1) in liver and fat cells
  - impaired insulin signaling on fat cells
HIV Management: The New Frontier

Vessels
- Increased systemic VLDL and triglyceride in circulation
- Shift to triglyceride-rich VLDL
- Increased systemic apolipoprotein C-II and apolipoprotein E
- Increased accumulation of CD16-dependent cholesterol ester in macrophages
- Decreased degradation of lipoprotein B
- Impaired fibrinolysis

Liver
- Increased hepatic glucose production?
- Decreased mitochondrial fatty acid oxidation (with nucleoside reverse-transcriptase inhibitor)
- Increased lipid accumulation and hepatic steatosis

Fat
- Increased lipolysis
- Decreased subcutaneous fat differentiation and increased apoptosis
- Decreased SREBP1-activated PPARγ expression
- Decreased SREBP1 nuclear localization (with protease inhibitor)
- Toxic effects on mitochondria and reduced PPARγ expression (with nucleoside reverse-transcriptase inhibitor)

Visceral fat hypertrophy

Muscle
- Decreased glucose transporter 4-mediated glucose transport (with protease inhibitor)
- Decreased glucose phosphorylation (P) secondary to increase in free fatty acids
- Increased intramyocellular lipid (P) secondary to decrease in adiponectin and intramyocellular fatty acid oxidation

Pancreas
- Increased insulin resistance
- Increased insulin secondary to resistance

Free fatty acids

Source: HIV Med © 2007 Blackwell Publishing
LIPODYSTROPHY

MASSIVE BUFFALO HUMP

Picture:
Courtesy of
Dr Harold Plitt,
vd Byl Park
Gauteng

October 2010
LIPODYSTROPHY

Pictures:
Courtesy of
Dr Harold Plitt,
vd Byl Park,
Gauteng

October 2010
Lipodystrophy: Buffalo Hump, Bull Neck, Fat loss in arms and legs; abdominal fat pad.

Courtesy: Dr Harold Plitt, October 2010
HIV and the CARDIOVASCULAR SYSTEM

Dr Dave Spencer  Right to Care The Helen Joseph Hospital Johannesburg and the SA HIV Clinicians’ Society
INCREASED DEPOSITION OF FAT

INCREASED TRUNKAL FAT
INCREASE IN ABDOMINAL FAT
BREAST ENLARGEMENT
DORSO-CERVICAL FAT DEPOSITS: BUFFALO HUMP

Not confined to d4T or ZDV
Seen with PI, NNRTI and NRTI combinations

Cause likely to be multi-factorial and includes the ARVs, cytokines, growth hormone and adiponectin
Lipoatrophy = thymidines (+EFV)

Fat accumulation = NRTIs and PIs (ritonavir)

Thymidines: stavudine, zidovudine

Changes in limb and central fat deposition are clinically visible in 20-35% of patients after approx. 12-24 months of combination ART.

LIPOATROPHY*

ASSOCIATED WITH THE NNRTIs

STAVUDINE >> ZIDOVUDINE

GS934: zidovudine >> tenofovir at wk 48-96
ACTG5142: stavudine >> zidovudine at wk 96
ACTG5142: more likely w. EFV >> LPV/r
ACTG384: NLF >> EFV

THE USE OF RITONAVIR SEEMS TO BE PARTIALLY PROTECTIVE

* Lipoatrophy = > 20% loss of body fat (arms) at the end of 96 weeks of study

Wohl DA, Brown T. Management of Morphologic Changes Associated with Antiretroviral Use in HIV-Infected Patients. JAIDS 2008;49 (Suppl 2):93-100
Within 6 weeks of starting d4T and ZDV significant changes occur in the expression of lipid and mitochondrial genes. The lipoatrophy that follows d4T and ZDV use promotes IR and hence contributes to hyperglycaemia.

Stavudine (d4T) and Zidovudine (ZDV)
Depletion of mitochondrial DNA (mtDNA) polymerase gamma(γ) is associated with NRTI activity and with adipocyte apoptosis and with ultrastructural changes within fat cells.

HIV infected people who have not yet started ARVs, demonstrate mtDNA depletion compared with healthy controls.


Cote HCF, Brumme ZL et al. *NEJM* 2002;346:811-20
Mitochondrial toxicity and the ARVs

Mitochondrial dysfunction leads to the accumulation of fatty acids.

The NRTIs viz. stavudine, didanosine, zidovudine, inhibit mitochondrial DNA polymerase γ

The Antiretroviral Drugs

The Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine
- Truvada
- Atripla
- Kivexa
- Zalcitabine

The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

The Protease Inhibitors (PIs)
- Amprenavir
- Atazanavir
- Darunavir
- Indinavir
- Lopinavir
- Ritonavir
- Saquinavir
- Tipranavir
- Nelfinavir

The Integrase Inhibitors (INSTIs)
- Raltegravir
- Elvitegravir

The HIV Entry Inhibitors
- GSK1349572/Dolutegravir
- Truvada
- Atripla
- Kivexa
- Zalcitabine
GYNAECOMASTIA

Efavirenz

Hypogonadism

Liver disease

Oestrogens

Picture: Per kind permission
Dr Harold Plitt
Vereeniging
Gauteng
Mutations
Non-suppressive ART regimens lead to viral resistance and viral load rebound. Initially the resistance mutations are single and few. But if therapy is not changed mutations increase. Multiple mutations lead to CROSS-RESISTANCE

ART is currently life-long. 100% adherence is essential. Ensure that drug toxicity is minimized.
10 years of HAART

20 to 30 tablets a day

One tablet once a day!
**What is ART SUCCESS?**

**SUSTAINED CD4 INCREASE and/or MAINTENANCE**

**UNDETECTABLE VIRAL LOAD**
- at least 1 log decrease in VL within 4-8 wk of starting ART
- decline to undetectable levels by 24 wk after starting ART

**WELLNESS:** continued clinical improvement

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Maartens G. SA HIV Clinicians Society ART Guidelines in Adults
SA J HIV Med 2008;29:19-31
metabolic side-effects of antiretroviral therapy

MANAGEMENT of METABOLIC and related DISORDERS

EXERCISE
QUIT SMOKING
DIET and WEIGHT CONTROL
STATINS and FIBRATES

ANTIRETROVIRAL ‘SWITCH’ REGIMENS

**Increased fat deposition**

| aerobic and resistance exercises with or without metformin: reduce central obesity - results in HIV+ve patients variable |
| Recombinant growth hormone (rGH): induction 4mg/D IMI maintenance 2mg/D |
| Surgical approach: |
| Liposuction: limited success, fat tends to return. Surgical excision: fat tends to return if underlying defect not corrected |
| Tesamorelin: GH-releasing factor |

Studies in HIV-positive persons demonstrate that endurance and resistance exercise can reduce visceral adipose tissue

STATINS

- First line therapy in HIV-infected patients with increased LDL-cholesterol

- Statins on their own seldom achieve the desired goal

- Preferred statins: pravastatin, atorvastatin, fluvastatin

  Not recommended: Lovastatin, simvastatin (drug interactions, acute rhadomyolysis)

  Rosuvastatin: insufficient data

Statins require CYP3A4 metabolism. PI-inhibition of CYP3A4 results in toxic serum levels of the statins (Prava does not use CYP3A4)
**Fibrates:** agents of choice for elevated TGL, fenofibrate once daily dosing, increased risks of toxicity when used together with statins

**Niacin:** modest improvement in LDL and HDL levels, slight worsening of markers of insulin resistance

**Fish oil:** significant improvement in TGL levels especially if used with the fibrates

**Ezetimibe:** a new drug that decreases GIT-related cholesterol absorption. No interaction w. CYP450 system. Decreases LDL by 20% in one small study of HIV+ve patients. ACTG 5209 study awaited
Acknowledgement to Right To Care and UNAIDS.