Metabolic Complications of Antiretroviral Therapy, 2014

Dr Dave Spencer Head Infectious Diseases
Helen Joseph Hospital Johannesburg South Africa
Picture: Patient with a Massive Buffalo Hump on ART (stavudine). Courtesy H.Plitt, vdByl Pk, 2010

Severely malnourished child. Not on ART. Courtesy C. Haupt, Soweto, 2009

PREVENTION
LIPODYSTROPHY: The external manifestation of an altered internal biochemical environment

PREVENTION
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.

What percentage of South African adults (≥15yr) are hypertensive viz. BP ≥140/90mmHg?

1. 63%
2. 50%
3. 20%
4. 10%
N=25,532 “interviews”

N=12,025 physical examinations by an MO

N=8,078 fasting blood samples tested

Study Timeline: 2012

Participants: broad sampling of the SA population

**CLINICAL EXAMINATION**

**PREHYPERTENSIVE**

viz. BP 120-139/80-89mmHg

= 10.4% of ≥15y

**HYPERTENSIVE**

viz. BP≥ 140/90mmHg

= 10.2% of ≥15y

What percentage of South African adults (≥15yr) are diabetic and/or have abnormally high glucose levels after a 2-hour glucose tolerance test?

1. 9%
2. 18%
3. 36%
4. 45%
SOUTH AFRICAN HEALTH AND NUTRITION EXAMINATION SURVEY (SANHANES) –
Media Release of the SA Human Sciences Research Council (HSRC) 6 August 2013

N=25,532 “interviews”
N=12,025 physical examinations by an MO
N=8,078 fasting blood samples tested
Study Timeline: 2012
Participants: broad sampling of the SA population

LIPIDS and GLUCOSE

High serum TC = 23.9%
High serum LDL-C = 28.8%
Low serum HDL-C = 47.9%

Impaired glucose homeostasis = 18.4%

Diabetes diagnosed on blood tests = 9.5%

accessed: 09/30/2014
What percentage of South African women are currently obese i.e. BMI $\geq$ 30kg/m²?

1. 15%
2. 27%
3. 39%
4. 45%
SOUTH AFRICAN HEALTH AND NUTRITION EXAMINATION SURVEY (SANHANES) –
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N=25,532 “interviews”
N=12,025 physical examinations by an MO
N=8,078 fasting blood samples tested

Study Timeline: 2012
Participants: broad sampling of the SA population

OBESITY

Mean BMI (males) = 23.6kg/m²
Mean BMI (females) = 28.9kg/m²

Increased waist circumference and waist-hip ratio = 20.2% males and 68.2% females

Obesity in females increased from 27% in 2003 to 39.2% in 2012

accessed: 09/30/2014
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

Risk of Myocardial Infarction According to Exposure to cART

D:A:D Study: Increased Risk of MI Associated With Recent ABC or ddl Use Remained After Additional Adjustment for Factors Influenced by ART

Association With Recent\textsuperscript{a} Didanosine Use

- No further adjustment\textsuperscript{b}
- Adjustment also for:
  - Latest CD4 cell count
  - Latest VL
  - Latest lipids
  - Latest blood pressure
  - Diabetes
  - Fat loss/gain
  - Latest glucose

Adjusted Relative Rate (95% CI) = 1.49

Association With Recent\textsuperscript{a} Abacavir Use

Adjusted Relative Rate (95% CI) = 1.90

\textsuperscript{a} Still using or stopped within last 6 months.

\textsuperscript{b} All data depicted were also adjusted for demographic factors, calendar year, cohort, CV risk factors that are unlikely to be modified strongly by ART use and cumulative exposure to other antiretroviral drugs.

SMART: Subgroup Analysis in Patients Not Receiving ART at Study Entry

HIV-infected patients with CD4+ cell count > 350 cells/mm³ (N = 5472)

Deferred Arm
Intermittent ART
(n = 2720; 228 not receiving ART at trial start)

Immediate Arm
Continuous ART
(n = 2752; 249 not receiving ART at trial start)

Study halted prematurely; mean follow-up: 18 mos

• Treatment definitions for subanalysis
  – Deferred: ART initiated when CD4+ cell count < 250 cells/mm³, CD4+ cell percentage < 15%, or HIV symptoms
  – Immediate: ART initiated immediately after randomization

• Primary endpoints
  – OD or death from any cause
  – Fatal or nonfatal OD
  – Serious non-AIDS events
  – Fatal and nonfatal OD plus serious non-AIDS events

SMART: Immediate ART Reduces Risk of Clinical Events

- Immediate group experienced substantially fewer events (opportunistic disease or serious non-AIDS events)
  - Excess risk associated with deferring therapy: 5.4 events/100 person-yrs

<table>
<thead>
<tr>
<th>Event, n (Rate per 100 Person-Yrs)</th>
<th>Deferred Arm (n = 228)</th>
<th>Immediate Arm (n = 249)</th>
<th>HR (DC/VS)</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD/death</td>
<td>15 (4.8)</td>
<td>5 (1.3)</td>
<td>3.5</td>
<td>1.3-9.6</td>
<td>.02</td>
</tr>
<tr>
<td>OD only</td>
<td>11 (3.5)</td>
<td>4 (1.1)</td>
<td>3.3</td>
<td>1.0-10.3</td>
<td>.04</td>
</tr>
<tr>
<td>Serious non-AIDS events</td>
<td>12 (3.9)</td>
<td>2 (0.5)</td>
<td>7.0</td>
<td>1.6-31.4</td>
<td>.01</td>
</tr>
<tr>
<td>Composite*</td>
<td>21 (7.0)</td>
<td>6 (1.6)</td>
<td>4.2</td>
<td>1.7-10.4</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Fatal and nonfatal OD plus serious non-AIDS events.

SMART Study and CV Events

- SMART: 5472 patients (84% on ART) randomized to continuation (viral suppression; VS) or CD4-guided treatment interruption (drug conservation; DC)

<table>
<thead>
<tr>
<th>Events</th>
<th>DC</th>
<th>VS</th>
<th>RH (DC/VS)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical MI, silent MI, CAD requiring invasive procedure or surgery, CVD death</td>
<td>48</td>
<td>31</td>
<td>1.57</td>
<td>1.00–2.46</td>
<td>0.05</td>
</tr>
<tr>
<td>+ Peripheral vascular disease, CHF, CAD requiring medication</td>
<td>76</td>
<td>52</td>
<td>1.49</td>
<td>1.04–2.11</td>
<td>0.03</td>
</tr>
<tr>
<td>+ Unobserved death from unknown cause</td>
<td>84</td>
<td>54</td>
<td>1.58</td>
<td>1.12–2.22</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Conclusion
- Discontinuation strategy associated with higher risk of CV disease

<table>
<thead>
<tr>
<th>First-Author and Year (Ref. #)</th>
<th>Design: Total number; (n)</th>
<th>Events: MI (n)</th>
<th>Duration of FU on ART</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Friis-Moller et al 2007 (1)</strong></td>
<td>Observational cohort. N=23,437, 94,469py</td>
<td>345 events (MI)</td>
<td>83m (median)</td>
<td>RR: 1.16 [95% CI, 1.09-1.23] per year of ART exposure; RR: 1.16 [95% CI, 1.10-1.23] per year of PI exposure RR: 1.05[95%CI, 0.98-1.13] per year of NNRTI exposure</td>
</tr>
<tr>
<td><strong>Lang et al. 2010 (3)</strong></td>
<td>Case-control nested database N=74,958, 298,156py</td>
<td>289 cardiac events vs. 884 controls</td>
<td>79 vs. 84 m</td>
<td>MI incidence: 1.24/1000PY OR cumulative exposure to PI except saquinavir: 1.53 [95%CI, 1.21-1.94]</td>
</tr>
<tr>
<td><strong>Worm et al. 2010 (20)</strong></td>
<td>Observational cohort N=33,308 178,835py</td>
<td>580 Cardiac events (MI)</td>
<td>NR</td>
<td>MI incidence: 3.2/1000PY [95%CI, 3.0-3.5) RR cumulative to IDV and LPV/r: 1.12 [95% CI, 1.07-1.18] and 1.13 [95% CI, 1.05-1.21] respectively RR exposure to ABC and ddI: 1.70 [95%CI, 1.17-2.47] and 1.41 [95%CI, 1.09-1.82] respectively</td>
</tr>
<tr>
<td><strong>Obel et al. 2007 (19)</strong></td>
<td>Database/medical records: no validation N=9271 before ART, N=13,593 post-ART</td>
<td>Cardiac ischemia: 14 events before ART and 57 after.</td>
<td>1.6y before ART; 5.2y after ART</td>
<td>After ART started the risk of MI became higher: RR 2.12 [95% CI,1.62-2.76] The risk of MI did not increase further during the initial 8y of ART</td>
</tr>
</tbody>
</table>

**Table. Risk for Coronary Heart Disease Among ART-Treated HIV-Infected Patients.**

HIV AND CORONARY HEART DISEASE

REDUCING RISK FACTORS MUST BECOME A ROUTINE IN THE CARE OF HIV-POSITIVE PATIENTS WHO NOW LIVE LONGER.

Natural History and Immunopathogenesis of HIV-1 Infection: starting at Acute HIV Infection.

A cytokine “storm” contributes to immune activation and CD4 loss and clinical signs and symptoms.

HIV-1 infection and replication

Causes of Immune activation

Anti-HIV Immune response
Ag stimulation: HIV & other

Massive CD4+ T cell depletion

Production of HIV proteins Gp120, nef

Viral reactivation

Bacterial translocation

Systemic immune activation adaptive and innate

M.Erasmus, UP. 2011
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 sub-mucosal 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.
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

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
Proposed Mechanisms for Accelerated Atherogenesis in HIV-infected Patients

VESS LUMEN

ENDOTHELIAL SURFACE OF VESSEL

INTIMAL SURFACE OF VESSEL WALL

SMOOTH MUSCLE LAYER OF VESSEL WALL

Smooth muscle cells

HIV

neutrophil

LDL

dysfunctional vascular endothelium

platelets

Macrophage-derived foam cell

T-CELL

Proliferation of smooth muscle cells

IFN-γ

IL-1, IL-6

TNF-α

IL-18

IL-12

Approximately 3 (14%) million Africans over the age of 50 years are living with HIV Infection.

Negin J, Cumming RG. HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. *Bull World Health Organ* 2010; 88: 1847-53
The projected growth of type II DM in sub-Saharan Africa between the years 2010 and 2030 is 98%.

Impaired glucose tolerance in the region is expected to rise by 75.8% from 26.9 million in 2010 to 47.3 million in 2030.

CONSERVATIVE PROJECTIONS FOR THE SUB-SAHARAN REGION IN 2030 PREDICT THAT

18.65 MILLION PEOPLE WILL HAVE DIABETES.

THE MAJORITY WILL HAVE TYPE II DM AND WILL BE OVERWEIGHT/OBESE

**Figure.** Trends in age-standardised mean fasting plasma glucose (FPG) by region between 1980 and 2008 for (A) men and (B) women.

Figure. Trends in Age-standardised diabetes prevalence by region between 1980 and 2008 for (A) men and (B) women.

Growth in DM prevalence in Africa is particularly among women.

Figure. Percentage growth in age-standardised diabetes prevalence, 1980–2008, by region. Data from reference 2; percentage change calculated by fitting linear model to all 29 annual age-standardised (WHO World Population) prevalence values from 1980 to 2008 for each region; diabetes defined by current American Diabetes Association definition.
The diagnosis of type 2 diabetes:

- a glycated hemoglobin value of 6.5% or more
- a fasting plasma glucose level of 126 mg/dL (7.0mmol/L) or more
- or a 2-hour plasma glucose level of 200mg/dL (11.1mmol/L) or more during an oral glucose tolerance test.

American Diabetes Association
Figure. Prevalence of diabetes mellitus and impaired glucose tolerance in community surveys in Africa. *1998 WHO criteria

Swiss HIV Cohort Study

DESCRIPTION:

Prospective cohort-study, clinic based. Started in 1988

N=6681 patients with at least 2 follow-up visits over at least 1 year

N= 123 newly diagnosed patients with diabetes while in the clinic viz. 4.42 cases per 1000 PYFU (95% CI, 3.71-5.28)

Current exposure to NRTI therapy, NRTI+PI combination therapy or NRTI+PI+NNRTI combination therapy increased the risk of developing DM in the univariable model with IRRs of 2.22 (1.11-4.45), 2.48 (1.42-4.31) and 3.25 (1.59-6.67) respectively

Figure. Incidence rate ratios (IRRS) for the development of new-onset type 2 diabetes mellitus (DM) based on 123 events among 6513 participants with 27,798 person-years of follow-up. Shown are associations with current receipt of specific drug classes and individual protease inhibitor (PI) and nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) combinations.
<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>ADVERSE METABOLIC EFFECT</th>
<th>IMPACT ON CORONARY HEART DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTEASE INHIBITOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOPINAVIR/r</td>
<td>Dyslipidemia+++; insulin resistance++</td>
<td>Cumulative exposure= an independent risk for MI</td>
</tr>
<tr>
<td>ATAZANAVIR/r</td>
<td>Dyslipidemia+; insulin resistance+</td>
<td>No data available: insufficient patients (numbers) exposed</td>
</tr>
<tr>
<td>DARUNAVIR/r</td>
<td>Dyslipidemia+; insulin resistance+</td>
<td>No data available: insufficient patients exposed</td>
</tr>
<tr>
<td>RITONAVIR</td>
<td>Dyslipidemia+++; insulin resistance+++</td>
<td>This drug is never used on its own i.e. a used as a pharmacological ‘booster’.</td>
</tr>
<tr>
<td>SAQUINAVIR</td>
<td>Dyslipidemia+; insulin resistance+</td>
<td>No associated risk for MI</td>
</tr>
<tr>
<td>INDINAVIR</td>
<td>Dyslipidemia and insulin resistance+++</td>
<td>Controversial results</td>
</tr>
<tr>
<td>AMPRENAVIR/r</td>
<td>Dyslipidemia+; insulin resistance+</td>
<td>No data available: insufficient numbers exposed</td>
</tr>
<tr>
<td>TIPRANAVIR/r</td>
<td>Dyslipidemia++; insulin resistance+</td>
<td>No data available: insufficient numbers exposed</td>
</tr>
<tr>
<td>NELFINAVIR</td>
<td>Dyslipidemia+; insulin resistance+</td>
<td>No associated risk for MI</td>
</tr>
</tbody>
</table>

Main classes of Antiretrovirals and Their Impact on Lipid and Glucose Metabolism and Coronary Heart Disease. + weak effect; ++ moderate effect; +++ important effect

### Main classes of Antiretrovirals and Their Impact on Lipid and Glucose Metabolism and Coronary Heart Disease. + weak effect; ++ moderate effect; +++ important effect


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<th>ADVERSE METABOLIC EFFECT</th>
<th>IMPACT ON CORONARY HEART DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NUCLEOTIDE/SIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTIs</td>
<td>Insulin resistance+: stavudine&gt;zidovudine; dyslipidemia with didanosine and stavudine</td>
<td>Two NRTIs viz. abacavir and didanosine have been associated with an increased risk for MI but results ‘controversial’</td>
</tr>
<tr>
<td><strong>NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Dyslipidemia variable with different members of this class: efavirenz but to a lesser degree than the Pis; nevirapine = a mild dyslipidemia but with increased HDL cholesterol</td>
<td>No association with an increased risk for MI</td>
</tr>
<tr>
<td><strong>INTEGRASE INHIBITORS (RALTEGRAVIR) and CCR5 CO-RECEPTOR INHIBITOR (MARAVIROC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No adverse metabolic effects reported</td>
<td>No data available: insufficient numbers exposed</td>
</tr>
</tbody>
</table>
LIFESTYLE MODIFICATION

Weight loss/diet:
Balanced diet rich in grains and legumes, <7% saturated fat and reduced trans fats + limited calories + foods with a high glycemic index

Exercise:
150 minutes of moderate-intensity aerobic exercise per week

Ismail-Beigi F. Glycemic Management of Type 2 Diabetes Mellitus. 
LIFESTYLE MODIFICATION

Weight loss/diet:

Abdominal circumference = risk predictor for type II DM
Excessive visceral fat = increased release of IL-6 and IL-34
i.e. inflammatory cytokines

PSYCHOLOGICAL:

- Set GOALS: 5-10% weight loss in the first 6m.
- Know the patients GOALS
- COMBINATION of approaches likely to be of greatest benefit

Ismail-Beigi F. Glycemic Management of Type 2 Diabetes Mellitus.  
DRUG MANAGEMENT OF DIABETES MELLITUS

METFORMIN
Contraindicated in renal and liver disease, cardiac failure and alcoholics. Slight risk of lactic acidosis. Care with dolutegravir: pushes up serum levels of metformin levels and increases toxicity. Metformin may worsen ART-related lipoatrophy.

Figure. Increasing complexity of the drug management of diabetes mellitus over time.

Oral drugs approved for treatment of hyperglycemia in type 2 diabetes.

Second-generation sulfonylureas:

- Glibenclamide
- Gliclazide
- Glimepiride
- Glipizide

Biguanide: Metformin

Peroxisome proliferator-activated receptor γ agonists: Thiazolidinediones:
- Pioglitazone
- Rosiglitazone

α-Glucosidase inhibitors: Acarbose; Miglitol; Voglibose

DPP4 inhibitors:

- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin
- Vildagliptin

GLIPTINS: CAN ADD TO METFORMIN

GLIFLOZINS: LOWER URINARY TRACT INFECTIONS

SGLT2 inhibitors:

- Canagliflozin
- Dapagliflozin

Glinides: Nateglinide; Repaglinide

Bile-acid-binding resins: Colesevelam

Dopamine-receptor agonists: Bromocriptine

WEIGHT GAIN + HYPOGLYCEMIA

Key areas to be addressed if diabetes is to be tackled in sub-Saharan Africa as identified by the International Insulin Foundation.

- Organisation of the health system
  - Prevention
    - Data collection
  - Diagnostic tools and infrastructure
    - Drug procurement and supply
- Accessibility and affordability of medicines and care
  - Training and availability of health-care workers
    - Adherence issues
  - Patient education and empowerment
- Community involvement and diabetes associations
  - Positive policy environment

Beran D, Yudkin JS. Diabetes care in sub-Saharan Africa. *Lancet* 2006; 368: 1689-95
### Are We Ready to Manage Africa’s HIV+ve Diabetics?

<table>
<thead>
<tr>
<th></th>
<th>Hospitals (n=176)</th>
<th>Health centres (n=92)</th>
<th>Dispensaries (n=67)</th>
<th>P value</th>
<th>Total</th>
<th>P value vs HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At least fair knowledge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>134 (76%)</td>
<td>74 (08%)</td>
<td>53 (79%)</td>
<td>0.67</td>
<td>261 (78%)</td>
<td>“</td>
</tr>
<tr>
<td>HTN</td>
<td>108 (61%)</td>
<td>57 (62%)</td>
<td>33 (49%)</td>
<td>0.52</td>
<td>198 (59%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DM</td>
<td>109 (62%)</td>
<td>42 (46%)</td>
<td>36 (54%)</td>
<td>0.24</td>
<td>187 (56%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Experienced</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>140 (80%)</td>
<td>67 (73%)</td>
<td>30 (45%)</td>
<td>0.01</td>
<td>237 (71%)</td>
<td>“</td>
</tr>
<tr>
<td>HTN</td>
<td>101 (57%)</td>
<td>19 (21%)</td>
<td>14 (21%)</td>
<td>0.001</td>
<td>134 (40%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DM</td>
<td>96 (55%)</td>
<td>6 (7%)</td>
<td>7 (10%)</td>
<td>&lt;.0001</td>
<td>109 (33%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Comfortable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>26 (15%)</td>
<td>13 (14%)</td>
<td>13 (19%)</td>
<td>0.78</td>
<td>52 (16%)</td>
<td>“</td>
</tr>
<tr>
<td>HTN</td>
<td>17 (10%)</td>
<td>8 (9%)</td>
<td>9 (13%)</td>
<td>0.84</td>
<td>34 (10%)</td>
<td>0.01</td>
</tr>
<tr>
<td>DM</td>
<td>14 (8%)</td>
<td>10 (11%)</td>
<td>8 (12%)</td>
<td>0.78</td>
<td>32 (10%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Table.** Present level of preparedness of human resources to ensure quality primary care for HIV, hypertension and diabetes at 24 health facilities in northwestern Tanzania, among 335 health-care workers by health facility level.

HYPERTENSION. HIV. AFRICA
THE HEART OF SOWETO STUDY

Cohort drawn from consecutive referrals to the cardiac unit at the CHBH in Soweto from Jan.1-Dec 31, 2006

N = 45 400 in-patients in the Department of Medicine of the CHBH in 2006


Study population:

N = 4162 confirmed with cardiovascular disease

N = 1593 (38%) newly diagnosed
N = 2569 (62%) previously diagnosed and on treatment
N = 74 (5%) HIV-positive

1593 new cases of cardiac disease

Primary diagnosis

897 HTN (56%)
310 lone HTN
310 cases
19% [95% CI 17-21]

844 CCF (53%)
296 dilated CMO (35%)
281 HTN heart failure (33%)
225 R heart failure (27%)
77 ischemic CMO (9%)
67 valvular heart failure (8%)
704 cases
44% [95% CI 42-47]

360 valvular heart dis/dysfunctn (23%)
208 rheumatic (58%)
103 functional (29%)
78 degenerative (22%)
268 cases
17% [95% CI 15-19]

165 coronary artery disease (10%)
28 CAD without risk factors (17%)
165 cases
10% [95% CI 8-12]

146 other diagnoses (9%)
67 pericardial effusn. (46%)
25 cardiac arrhythmia (17%)
22 congenital HD (15%)
16 stroke (11%)
146 cases
9% [95% CI 8-11]
ALMOST HALF OF THOSE PATIENTS DIAGNOSED WITH HYPERTENSION IN THE ABSENCE OF CLINICAL HEART DISEASE WERE OBESE. That black African women were most likely to be obese both in this hospital cohort and in the general Sowetan community, is noteworthy in view of the male dominance and older age of similar cohorts in developed countries.

# THE HEART OF SOWETO STUDY (2006)

<table>
<thead>
<tr>
<th>Profile</th>
<th>All (n=1593)</th>
<th>HTN (n=310)</th>
<th>CCF (n=704)</th>
<th>Valve dis (n=268)</th>
<th>CAD (n=165)</th>
<th>Other (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>52.8 (17.1)</td>
<td>58.3 (15.3)</td>
<td>55.1 (16.2)</td>
<td>45.7 (18.2)</td>
<td>56.7 (12.4)</td>
<td>38.0 (16.6)</td>
</tr>
<tr>
<td>Black African</td>
<td>1359 (85%)</td>
<td>265 (86%)</td>
<td>640 (91%)</td>
<td>243 (91%)</td>
<td>77 (47%)</td>
<td>134 (92%)</td>
</tr>
<tr>
<td>Women</td>
<td>939 (59%)</td>
<td>199 (64%)</td>
<td>409 (58%)</td>
<td>179 (67%)</td>
<td>68 (41%)</td>
<td>84 (58%)</td>
</tr>
<tr>
<td><strong>High cholesterol</strong></td>
<td>159 (22%)</td>
<td>54 (38%)</td>
<td>45 (17%)</td>
<td>16 (21%)</td>
<td>37 (35%)</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>661 (41%)</td>
<td>112 (36%)</td>
<td>327 (46%)</td>
<td>84 (31%)</td>
<td>84 (51%)</td>
<td>54 (37%)</td>
</tr>
<tr>
<td>Renal dysf.</td>
<td>115 (10%)</td>
<td>23 (10%)</td>
<td>51 (10%)</td>
<td>20 (8%)</td>
<td>16 (11%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>156 (13%)</td>
<td>30 (12%)</td>
<td>64 (11%)</td>
<td>22 (12%)</td>
<td>7 (6%)</td>
<td>33 (28%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>165 (10%)</td>
<td>41 (13%)</td>
<td>66 (9%)</td>
<td>13 (5%)</td>
<td>35 (21%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>HIV+ve*</td>
<td>74 (5%)</td>
<td>4 (1%)</td>
<td>35 (5%)</td>
<td>10 (4%)</td>
<td>2 (1%)</td>
<td>23 (16%)</td>
</tr>
<tr>
<td>NYHA Class III/IV</td>
<td>486 (31%)</td>
<td>84 (27%)</td>
<td>255 (36%)</td>
<td>63 (24%)</td>
<td>32 (19%)</td>
<td>52 (36%)</td>
</tr>
</tbody>
</table>

* HIV test = only “if clinically indicated and consent given”

Methods:

Prospective study of HTN over 24 months on ART

ART-naïve adults April 2004-2011 n=17 378 patients

Patients with HTN at ART-initiation excluded:
  n = 5002 (28.8%) of 17 378 clinic patients

HTN defn.: systolic BP> 140 and/or diastolic BP>90mmHg
  and characterized as mild (140-159.9/90-99.9)
  or moderate/severe (≥160/≥100)

### PREDICTORS OF HYPERTENSION IN HIV-POSITIVE ADULTS OVER 24 MONTHS ON ART IN SOUTH AFRICA

<table>
<thead>
<tr>
<th>Age</th>
<th>HR for HTN at 24m [95%CI]</th>
<th>HR for mild HTN at 24m [95%CI]</th>
<th>HR for mod/severe HTN at 24m [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49.9y</td>
<td>1.6 [1.4-1.7]</td>
<td>1.5 [1.4-1.7]</td>
<td>1.7 [1.2-2.3]</td>
</tr>
<tr>
<td>≥50y</td>
<td>2.5 [2.2-2.9]</td>
<td>2.3 [2.0-2.6]</td>
<td>4.3 [3.1-6.0]</td>
</tr>
</tbody>
</table>

**BMI at ART start**

<table>
<thead>
<tr>
<th>BMI at ART start</th>
<th>HR for HTN at 24m [95%CI]</th>
<th>HR for mild HTN at 24m [95%CI]</th>
<th>HR for mod/severe HTN at 24m [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29.9</td>
<td>1.5 [1.3-1.7]</td>
<td>1.5 [1.3-1.7]</td>
<td>1.6 [1.2-2.3]</td>
</tr>
<tr>
<td>30-34.9</td>
<td>1.8 [1.5-2.2]</td>
<td>1.8 [1.5-2.2]</td>
<td>1.9 [1.1-3.3]</td>
</tr>
</tbody>
</table>

No correlation with other variables viz. initiating ART, sex, CD4 count, HB and WHO Stage at initiation of ART.

OUTCOME:

20% of patients in this cohort (n = 12,376 patients) developed HTN over 24 months while taking ART.

**Obese patients and those older than 40 years should be targeted for frequent BP monitoring and for identification of additional cardiac risk factors.**

CLINICAL OUTCOME in patients with OBESITY or HYPERTENSION IN A SOUTH AFRICAN HIV-POSITIVE COHORT

Methods:

Prospective cohort study
ART naïve adults starting ART April 2004-2009
Cox regression re. mortality and loss to follow-up among patients with obesity and HTN

Total patients n = 9693
Female n = 6095 (62.9%)
Age median (IQR) = 36yr (31.2-42.5)
Baseline CD4 at ART initiation:
CD4 >350 n = 86 (0.9%)
CD4 200-350 n = 816 (8.4%)
CD4 101-200 n = 3427 (35.4%)
CD4 51-100 n = 2078 (21.4%)
CD4 ≤50 n = 3286 (33.9)

Brennan AT, Fox MP, Maskew M, Sanne I, et al. Obesity or Hypertension at ART Initiation and Outcomes Among HIV Patients in South Africa. CROI Boston, February 2014, Poster #803

HIV AND HYPERTENSION: HELEN JOSEPH HOSPITAL
CLINICAL OUTCOME in patients with OBESITY or HYPERTENSION IN A SOUTH AFRICAN HIV-POSITIVE COHORT

RESULTS:

**DEATH**

- BMI $> 30$: HR 1.8 [1.3-2.6 95% CI] at 12m
- BMI $> 30$: HR 1.3 [1.0-1.8 95% CI] at 48m
- Mod/severe HTN at ART initiation: HR 1.4 [1.0-2.1 95% CI] at 48m

**LOSS TO FOLLOW-UP**

- BMI $> 30$: HR 0.6 [0.4-0.9 95% CI] at 12m
- BMI $> 30$: HR 0.7 [0.6-0.9 95% CI] at 48m

**CD4 RESPONSE**

Increase of CD4 cells at 12 and 48m in those with BMI $\geq 30$ level*

- 8.6 cells at 12m [7.3-24.5 95% CI]
- 40.7 cells at 48m [12.4-93.8]

*92% initiated on d4T+3TC+EFV

Brennan AT, Fox MP, Maskew M, Sanne I, et al. Obesity or Hypertension at ART Initiation and Outcomes Among HIV Patients in South Africa. CROI Boston, February 2014, Poster #803

HIV AND HYPERTENSION: HELEN JOSEPH HOSPITAL
CLINICAL OUTCOME in patients with OBESITY or HYPERTENSION IN A SOUTH AFRICAN HIV-POSITIVE COHORT

BY 48M, 1001 (10%) OF PATIENTS HAD DIED and 2069 (21%) were lost to follow-up

Patients with a BMI>30 = increased mortality over 48m on ART but lower LTFU and an improved CD4 cell recovery

Patients with a moderate or severe hypertension had a slight increase in mortality (40%) but no relationship with LTFU, CD4 response or having a detectable viral load

Brennan AT, Fox MP, Maskew M, Sanne I, et al. Obesity or Hypertension at ART Initiation and Outcomes Among HIV Patients in South Africa. CROI Boston, February 2014, Poster #803
Figure. Estimated decrease in blood pressure mediated by non-pharmacological anti-hypertensive interventions.

A CROSS-SECTIONAL MULTICENTER STUDY of 173 HIV-infected between ages 14-24 yr all of whom acquired infection sexually.

4 CATEGORIES:

ART NAÏVE
N = 85

ON NNRTI-BASED ART
N = 33

ON PI-BASED ART
N = 36

ON NON-NNRTI or PI-BASED ART
N = 19

GOAL OF THE STUDY:
Determine the nature and prevalence of biochemical changes in lipid and glucose metabolism and body composition in young HIV infected women on and off antiretroviral medication

NEW AHA/AHA GUIDELINES: CHOLESTEROL LEVELS and CARDIOVASCULAR RISK

For primary prevention for those who are currently free of cardiovascular disease, statin therapy is recommended for persons with total cholesterol levels above 190mg/dL (4.90mmol/l) and for those with diabetes whose LDL cholesterol is 70mg/dL (1.8mmol/l) or higher.
<table>
<thead>
<tr>
<th>HMG-Co-A Reductase Inhibitor</th>
<th>Antiretroviral Agent:</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATOVASTATIN</td>
<td>All PIs</td>
<td>Use lowest possible starting dose and monitor carefully: rhabdomyolysis</td>
</tr>
</tbody>
</table>

**NNRTIs reduce the atorvastatin, simvastatin and lovastatin blood levels by 40-80%**

<table>
<thead>
<tr>
<th>NNRTI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Adjust atorvastatin dose according to lipid response. Don’t exceed max dose</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>Adjust dose according to lipid response. Don’t exceed max dose.</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>No data but decreased atorvastatin conc. expected. Adjust accord. 2 lipid response.</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>No interaction expected. No dose adjustment necessary.</td>
<td></td>
</tr>
</tbody>
</table>

NB. When using statins with NNRTIs, work up to maximal recommended doses of the statin but do not exceed these doses

---

Clinically Relevant Interactions With Concomitant use of HMG Co-A Reductase Inhibitors and Antiretrovirals

<table>
<thead>
<tr>
<th>HMG-Co-A Reductase Inhibitor</th>
<th>Antiretroviral Agent:</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRAVASTATIN</td>
<td><strong>PIs</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Darunavir/r</td>
<td>Potential for signific. increase in prava level: start with lowest dose and monitor closely</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/r</td>
<td>Prava conc. increases: monitor carefully</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td>Efavirenz</td>
<td>Adjust prava dose accord 2 lipid response</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>No interaction</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
<td>No data</td>
</tr>
</tbody>
</table>

NB. When using statins with NNRTIs, work up to maximal recommended doses of the statin but do not exceed these doses.

Clinically Relevant Interactions With Concomitant use of HMG Co-A Reductase Inhibitors and Antiretrovirals

<table>
<thead>
<tr>
<th>HMG-Co-A Reductase Inhibitor</th>
<th>Antiretroviral Agent:</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>PIs</td>
<td>CONTRAINDIicated</td>
</tr>
</tbody>
</table>

NNRTIs reduce the atorvastatin, simvastatin and lovastatin blood levels by 40-80%

- **NNRTI**
  - Efavirenz: Adjust dose of simvastatin according to lipid response
  - Etravirine: Do not exceed maximum recommended dose
  - Nevirapine
  - Rilpivirine

Where statin concentrations are decreased, use of potent statins such as simvastatin, atorvastatin and rosuvastatin may be more likely to achieve lipid goals.

**Clinically Relevant Interactions With Concomitant use of HMG Co-A Reductase Inhibitors and Antiretrovirals**

Ezetimibe is metabolized in the small intestine and liver via glucuronide conjugation and excreted in the bile. Half-life is 22 hours. It does not interfere with cytochrome P450 enzymes. Concomitant use of antacids and cholestyramine will reduce the absorption of ezetimibe.

No anticipated drug interactions with the NNRTIs, PIs or Integrase inhibitors.

However absorption of drugs from the GIT may be reduced:
monitor carefully.

**ATAZANAVIR**
MANAGEMENT of METABOLIC and related DISORDERS

EXERCISE
Aerobic & Resistance

QUIT SMOKING

DIET and WEIGHT CONTROL

STATINS and FIBRATES
Pravastatin, Atorvastatin, Bezafibrate


ANTIRETROVIRAL ‘SWITCH’ REGIMENS
Avoid thymidine NRTIs and ddl; NVP may be better than EFV; ATV and DRV likely to be better than LPV/r; Raltegravir ‘safe’; maraviroc

MISCELLANEOUS
Growth hormone, Testosterone; Cosmetic surgery and Liposuction