Diabetes, Metabolic Syndrome & HIV

Mike Reid

MD MA MRCP
Outline

• Review recent advances in understanding of diabetes in HIV infection
• Describe the impact of HIV and ARVs on pathogenesis of diabetes and diabetic complications
• Discuss importance of prevention, screening and treatment of diabetes in people with HIV in Southern Africa
DEFINITIONS

HIV and DM
# Diabetes Mellitus: Definitions

<table>
<thead>
<tr>
<th></th>
<th>Fasting plasma glucose (mg/dl)</th>
<th>Oral glucose tolerance test (OGTT) (mg/dl)*</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>&gt;7.0 OR ≥11.1</td>
<td></td>
<td>&gt;6.5%</td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance (IGT)</strong></td>
<td>&lt;7.0 AND 7.8 -11.0</td>
<td>Pre-diabetes</td>
<td></td>
</tr>
<tr>
<td><strong>Impaired fasting glucose (IFG)</strong></td>
<td>6.1 – 6.9 AND &lt;7.0</td>
<td>5.7-6.4%</td>
<td></td>
</tr>
</tbody>
</table>

**OGTT indicated:**
- In asymptomatic high-risk individuals
- If FPG is ≥ 5.6 - <7.0 mmol/l
- If random plasma glucose ≥ 5.6 - <11.1† (on screening)

1 WHO, 2009
IFG/IGT – Represent prodromal state
4-6 times risk of developing DM
70% go onto to develop DM
Associated with increased CV morbidity & mortality

*IGT = impaired glucose tolerance
IFG= impaired fasting glucose
HIV and DM – Part 1

EPIDEMIOLOGY & PATHOGENESIS
Even in Africa, obesity a burgeoning problem – Health – Diet and nutrition | NBC News

GSK study: 61% South Africans overweight

MRC study:
56% of women BMI>25
26% of men BMI>25
Prevalence estimates of diabetes (20-79 years), Africa Region, 2011

International Diabetes Foundation, 2011
## Diabetes Prevalence in South Africa

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>N</th>
<th>Age (years)</th>
<th>Method</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erasmus (2001)</td>
<td>Urban</td>
<td>374</td>
<td>&gt;20</td>
<td>OGTT</td>
<td>4.5%</td>
</tr>
<tr>
<td>Omar (1993)</td>
<td>Urban</td>
<td>499</td>
<td>&gt;15</td>
<td>OGTT</td>
<td>5.3%</td>
</tr>
<tr>
<td>Levitt (1993)</td>
<td>Urban</td>
<td>729</td>
<td>&gt;30</td>
<td>OGTT</td>
<td>8.0%</td>
</tr>
<tr>
<td>Mollentze (1995)</td>
<td>Urban</td>
<td>758</td>
<td>&gt;25</td>
<td>OGTT</td>
<td>6.0%</td>
</tr>
<tr>
<td>Motala (2008)</td>
<td>Rural</td>
<td>1021</td>
<td>&gt;15</td>
<td>OGTT</td>
<td>1.5%</td>
</tr>
<tr>
<td>Alberts (2005)</td>
<td>Urban</td>
<td>2106</td>
<td>&gt;30</td>
<td>FBG</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Conservative estimates: 6.5% of adults have diabetes – but age adjusted prevalence studies from urban populations indicate prevalence >13%
6 reasons why DM is on the rise in South Africa
HIV and DM

1 Levitt, Am J Clin Nutr, 2011
### DM and HIV in Africa

Age-adjusted prevalence of diabetes among PLWH in Southern Africa

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (years)</th>
<th>On ART? (Y/N)</th>
<th>Years on HAART</th>
<th>DM</th>
<th>IFG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>South Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dave (2011)</td>
<td>406</td>
<td>34 (mean)</td>
<td>N</td>
<td></td>
<td>3.4%</td>
<td>18.5%</td>
</tr>
<tr>
<td></td>
<td>443</td>
<td>33 (mean)</td>
<td>Y</td>
<td>1.2</td>
<td>2.3%</td>
<td>23.5%</td>
</tr>
<tr>
<td><strong>South Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Julius (2011)</td>
<td>304</td>
<td>18-45</td>
<td>Y</td>
<td>1</td>
<td>1.3%*</td>
<td></td>
</tr>
<tr>
<td><strong>Botswana</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hatsu (2009)</td>
<td>610</td>
<td>&gt;15</td>
<td>N</td>
<td>0</td>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;40</td>
<td>N</td>
<td>0</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td><strong>Malawi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muronya (2011)</td>
<td>174</td>
<td>&gt;18</td>
<td>Y</td>
<td>1</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Rwanda</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutimara (2007)</td>
<td>571</td>
<td>&gt;18</td>
<td>Y</td>
<td>&gt;6 months</td>
<td>16-18%</td>
<td></td>
</tr>
<tr>
<td><strong>Kenya</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuthu (2008)</td>
<td>295</td>
<td>&gt;18</td>
<td>Y</td>
<td>&gt;1 yr</td>
<td>1.5%</td>
<td>21.4%</td>
</tr>
<tr>
<td><strong>Benin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zannou (2009)</td>
<td>79</td>
<td>&gt;18</td>
<td>Y</td>
<td>&gt;1 yr</td>
<td>1.5%</td>
<td>34-37%</td>
</tr>
</tbody>
</table>

* Young population. Yet >50% had lipid abnormalities
Multifactorial Aetiology of Diabetes in HIV
Multifactorial Aetiology of Diabetes in HIV
Risk Factors – Obesity

D:A:D cohort:¹ (n=33,389) 130,151 person years of patient follow up

Rates of DM:

- **x2 in overweight** (BMI 26-30 kg/m²)
- **x4 in obesity** (BMI >30kg/m²)

ANSR-CO8 Cohort²

- **HR for DM 1.91** (CI 1.22-2.99) for overweight participants
- **HR for DM 2.85** (CI 1.35-6.04) for obese participants

Waist-hip ratio more predictive than BMI

Increased sex-appropriate waist-hip ratio x3.87 risk of DM

¹ – De Wit, Diabetes Care, 2008; ² – Capeau, AIDS, 2012
Risk Factors – Obesity

Many determinant of obesity are same for HIV+ and HIV-
- Genetics – 25%¹
- Intra-uterine and early life influences
- Physical activity²
- Education³
- Sense of Coherence⁴
- Parity⁵

Implications:
RSA:
- 56% Women obese or overweight⁶
- 29% Men obese or overweight ⁶

No data available on HIV infected population in RSA

Risk Factors – Age

Implications:

Estimated 3 million Africans with HIV > 50 years\(^3\)

In RSA approx 20% of all HIV infected persons are > 50 years\(^4\)

**HR 3.6** in patients> 50 years

(95% CI 2.22-5.92)

Risk Factors – Sex

• D:A:D study\textsuperscript{1}:
  – Male sex associated with \textbf{60\% higher risk} of diabetes compared to women

• WIHS study\textsuperscript{2}:
  – HIV uninfected more obese, yet HIV-infected \textbf{x2} as likely to have DM

\textbf{Take home message}: Women on HAART have lower risk of DM compared to men, but DM develops with less adiposity and drug exposure compared to men

1 – De Wit, Diabetes Care, 2 – Justmann, JAIDS, 2003
Other Risk Factors

- Dyslipidemia\(^1\)
- HCV co-infection\(^2\)
- Vitamin D deficiency\(^3\)
- Sex hormone levels\(^4\)
- Concomitant medications
  - Corticosteroids
  - Pentamidine
  - Atypical antipsychotics

1 – De Wit, Diabetes Care, 2008.
2 – Milner, Gastroenterology, 2010.
4 – Szep, JAIDS, 2011.
5 – Monroe, JAIDS, 2011.
Multifactorial Aetiology of Diabetes in HIV

Host

Medication

Disease
Risk factors – CD4 nadir

- **MAC Study**¹ (n=710 HIV+): **Lower = Increased risk**
  CD4 nadir<300 associated with RR 1.67 (CI 1.0-2.8) compared to CD4 nadir>300

- **Botswana**² (54 DM vs 108 non DM): **Higher = Increased risk**
  DM associated with higher CD4 nadir (CD4 156 vs CD 118, p<0.05)

- **ANSR-CO8 Cohort**³: **No difference in DM risk**
  No difference in DM incidence with CD nadir <200 or >200 (p0.67)

Risk factors – Viral

• Patients with untreated HIV have increased dyslipidemia\textsuperscript{1-3}
  – Elevated TG
  – Low HDL-C
  – Low LDL-C (relatively high small dense LDL-C)

• Patients with untreated HIV also have increased bio-inflammatory markers

Do these factors increase risk of insulin resistance or DM in HIV+ not on HAART?

Risk factors
HIV duration or Viraemia

• D:A:D Cohort\(^1\)

No association
RR per additional year: 0.98 (CI 0.96-1.00); p=0.09

• ANSR-CO8 Cohort\(^2\)

No association between VL and incidence of DM
Incidence 14.3/1000 when VL<5000, 15.2/1000 when VL>100000 (p=0.72)

1- De Wit, Diabetes Care, 2008. 2 –Capeau, AIDS, 2012
Multifactorial Aetiology of Diabetes in HIV
Diabetes Incidence in the Multicenter AIDS Cohort Study

- Incidence analysis on 680 males
  - BL fasting glucose: ≤ 5.44 mmol/L
  - No diabetes history (by self-report)
  - Median follow-up: 2.3 years

- **4-fold increase** in rate of incident diabetes in HAART-treated cohort vs HIV-negative group
  - 4.7 cases/100 person-years for HIV-positive patients on HAART vs 1.4 cases/100 person-years for HIV-negative cohort
  - **RR: 4.11** (95% CI: 1.85-9.16; \( P < .001 \))

**MAC Study Take Home Message:**
Initiating HAART significantly increased risk of DM
4 fold increase in DM on HAART cf to HIV negative
HAART – mechanism of diabetogenesis

Indirect effects of the drugs
1. Return to health phenomenon
2. Body Fat Partitioning disorders

Direct effects of specific drugs
1. PIs – inhibiting GLUT4 / reduced β-cell activity
2. NRTIs – mitochondrial toxicity
3. NNRTIs - ?
HAART
Direct Effects
Risk Factor: NRTIs

Direct effects

• Potential for mitochondrial toxicity – lipodystrophy syndrome

Indirect effects

• FFA accumulation in muscle and liver ("systemic steatosis")
  – Effects of inflammatory cytokines
Risk Factor: NRTIs

MAC Study Take Home Message:
• Exposure to **NRTIs** most strongly correlated with surrogates of insulin resistance (OR 1.08; 95% CI 1.02-1.13) after controlling for age, BMI, CD4 count
• **Stavudine** associated with highest risk of hyperinsulinemia (OR 1.2; 95% CI 1.2-1.3)

## Risk Factor: NRTI

<table>
<thead>
<tr>
<th>Cohort</th>
<th># on HAART</th>
<th>Location</th>
<th>Diagnosis</th>
<th>Years of follow up</th>
<th>Incidence (per 1000 person years of FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D:A:D1</td>
<td>33389</td>
<td>Multi-country FPG</td>
<td></td>
<td>5.72 (5.31 - 6.31)</td>
<td></td>
</tr>
<tr>
<td>WIHS2</td>
<td>2218</td>
<td>USA HOMA-IR &gt;3</td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>ANSR-CO84</td>
<td>1281</td>
<td>France</td>
<td>OGTT</td>
<td>14.1 (11.6 - 17.9)</td>
<td></td>
</tr>
</tbody>
</table>

### Summary: NRTI

Risk: d4T > AZT > 3TC/FTC  
Related to mitochondrial toxicity  
Cumulative exposure increases risk of IR

1 – De Wit, Diabetes Care, 2008.  
2 - Tien, JAIDS, 2008.  
3. Hassa, CID, 2011
Risk Factor: Protease Inhibitors

- Insulin resistance: mostly commonly seen with RTV/IDV/NFV\(^1\)

Direct effects of PIs
- Some PIs inhibit GLUT4, the major glucose transporter in fat and muscle (IDV, LPV/RTV)\(^2\)
- Reduced beta cell function: Ritonavir reported to reduce insulin synthesis between 25-50\%\(^3\)
- Inhibition of PPAR-\(\gamma\) activity leading to reduced adipocyte differentiation\(^4\)

Indirect effects
- Increased central obesity +/- lipodystrophy\(^4\)
- Dyslipidemia leading to metabolic syndrome\(^5\)

# Risk Factor: Protease Inhibitors

## Hyperinsulinemic Euglycemic Clamp Studies

<table>
<thead>
<tr>
<th>PI</th>
<th>N</th>
<th>HIV Status</th>
<th>Treatment duration</th>
<th>Δ in Insulin sensitivity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r (Noor 2004)</td>
<td>20</td>
<td>-</td>
<td>5 days</td>
<td>-24</td>
<td>0.008</td>
</tr>
<tr>
<td>LPV/r (Noor, 2006)</td>
<td>25</td>
<td>-</td>
<td>10 days</td>
<td>-25</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>LPV/r (Randal, 2007)</td>
<td>12</td>
<td>+</td>
<td>4 wks</td>
<td>-0.91</td>
<td>NS</td>
</tr>
<tr>
<td>LPV/r (Pao 2010)</td>
<td>8</td>
<td>-</td>
<td>4 wks</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>
## Risk Factor: PI

<table>
<thead>
<tr>
<th>Cohort</th>
<th># on HAART</th>
<th>Location</th>
<th>Diagnosis</th>
<th>Years of follow up</th>
<th>Incidence (per 1000 person years of FU)</th>
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<td>D:A:D1</td>
<td>33389</td>
<td>Multi-country FPG</td>
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<td></td>
</tr>
<tr>
<td>ANSR-CO84</td>
<td>1281</td>
<td>France OGTT</td>
<td>10</td>
<td>14.1 per 100 Pys (11.6 - 17.9)</td>
<td></td>
</tr>
</tbody>
</table>

### Summary: Protease Inhibitors

- Dose dependent risk
- Mechanism - dyslipidemia
- Withdraw drug and risk of IR drops

Risk Factor: NNRTIs

- D:A:D, CO8, MAC – no association between NNRTIs and Insulin Resistance

**NNRTIs: 2 questions**

1. **How do we explain the differences?**
   - African pharmacogenetics
   - Unexplained confounders
     - Lipodystrophy
     - Co-administration with d4T

2. **Clinically meaningful association?**

Diabetes Pathogenesis
Summary

Host
- Obesity
- Lipodystrophy
- Dyslipidemia
- Physical Inactivity
- Genetics
- Age
- Psychosocial factors

Medication
- NNRTIs
- NRTIs
- PIs

Disease
- HIV
- Viremia
- Inflammation

Diet
- Physical Inactivity

Drugs
- NRTIs

Genetics
- Dyslipidemia

Inflammation
- Host

Psychosocial factors
- Age
Healing is a matter of time, but it is also a matter of opportunity.
Hippocrates, 460 BC

HIV and DM: Part 2
Treatment & Management
## Guidelines for screening

<table>
<thead>
<tr>
<th>Country</th>
<th>DM Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEMDSA (2012)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Every 6 months on ARV treatment</td>
</tr>
<tr>
<td>SAHIVSoc (2012)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Glucose should be assessed ‘serially.’ 3 months after starting PI then annually if normal</td>
</tr>
<tr>
<td>United States (2011)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Before and after starting ARV 3-6 months after initiation Every 12 months thereafter</td>
</tr>
</tbody>
</table>

### Recommendations: At least annually for all patients on HAART and especially those with obesity, lipodystrophy, FH, on D4T or PIs

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**Brief Recap: Pathogenesis of Diabetes**

*IGT = impaired glucose tolerance
*IFG= impaired fasting glucose

**Plasma Glucose**
- 120 (mg/dL)

**Relative β-Cell Function**
- 100 (%)

**Years of Diabetes**
- -20
- -10
- 0
- 10
- 20
- 30

**Graphs**
- **Post-meal Glucose**
- **Fasting Glucose**
- **Insulin Resistance**
- **Diabetes**

*IGT = impaired glucose tolerance
IFG = impaired fasting glucose
Management of DM/IR in HIV patients

Don’t just screen – INTERVENE¹

1. Lifestyle Modifications
2. Medical management: metformin, TZDs
3. Δ of HAART: D4t, LPV
4. Screen for and manage complications

1. Lifestyle Modifications

3234 with IR (IGT):

Prevention program:
150 minutes/week of exercise and

Weight loss of 5-10%:\textsuperscript{2}
Reduces HbA1c by 0.5-1%
Increases life expectancy by 2-4 years

Regular exercise:\textsuperscript{3}
39-70% reduction in CVD morbidity over a 15 year period

1. Lifestyle Modifications

HIV+ adults (n=62) on ART with confirmed metabolic syndrome

“Those who do not make time for exercise will eventually have to make time for illness”

Earl of Derby 1863

2. Insulin sensitizing agents: metformin, TZDs
Metformin* in pre-diabetes Reduces Lipodystrophy:

<table>
<thead>
<tr>
<th>Change in Insulin</th>
<th>Change in Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have data here.</td>
<td>Have data here.</td>
</tr>
</tbody>
</table>

**Take Home Message:** In patients with pre-diabetes/metabolic syndrome, short term metformin significantly reduced mean insulin levels and visceral abdominal fat.

*500 mg BID  
N = 26, 3 month study duration

Metformin in pre-diabetes reduces risk cardiovascular risk\textsuperscript{1}

Take Home Message: Metformin to HIV+ with MS significantly reduced CAC scores, surrogate for atherosclerosis

Fitch, K, AIDS, 2012
TZDs in pre-diabetes: Impact on lipodystrophy and IR

✔ Rosiglitazone associated with increases in fat deposition for patients with lipoatrophy (N = 28)\(^1,2\)

✔ Rosiglitazone PLUS Exercise associated with improvements in insulin resistance in HIV+ on HAART (N=44)\(^3\)

Take home message: possible effect in reducing lipoatrophy, but given adverse effects probably best reserved for patients with frank DM and no evidence of CHF

3. Δ of HAART: D4t, LPV

SWITCHING PIs:
Older studies demonstrated that switching from PIs to an NNRTI was associated with significant improvements in fasting insulin resistance index

- NVP: decrease of 45%; $P = .0001^5$
- EFV: decrease of 28%; $P = .03^6$

4. Screen for and manage complications

• Nephropathy
  – HIV infected patients with DM: x2 rates of albuminuria to HIV infected non-DM (34% vs 13%, P=0.005)\(^1\)
  – Exposure to ABC associated with increased risk of albuminuria\(^1\)
  – Presence of DM independent risk factor for ESRD in HIV-infected cohort\(^2\)

• Retinopathy
  – Malawi study: retinopathy disease severity not associated with HIV status or VL\(^3\)

• Cardiovascular disease
  – D:A:D – Diabetes associated with x2.4 rates of coronary artery disease\(^4\)

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DM and HIV Service Delivery: Quality of Care
Management of DM in HIV patients: ‘Ensuring quality care’

Uncontrolled hyperglycemia in 33%, Suboptimal LDL control in 34%

1. Saitlin, AIDS Patient Care, 2011
Management of DM in HIV patients: ‘delivering quality care’

HIV HEART cohort:¹ (n=803;5% diagnosed with DM)
Only 56% (23/41) of patients were on DM meds
41% (42/102) of eligible patients were on anti-platelets

IMPLICATIONS
Implementing standard DM care in HIV infected patients is challenging in settings where treatment barriers are not expected.
Big barrier is CLINCIAL INTERTIA²

DM: the next big challenge for TB control?¹

¹ Harries, IJTL, 2011
## Importance of HIV and DM as risk factors for Tuberculosis

<table>
<thead>
<tr>
<th>Region</th>
<th>HIV</th>
<th>DM</th>
<th>Smoking</th>
<th>Malnourishment</th>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>HIV</td>
<td>PAF</td>
<td>RR</td>
<td>PAF</td>
</tr>
<tr>
<td></td>
<td>HIV%</td>
<td>PAF%</td>
<td>RR</td>
<td>DM%</td>
<td>PAF%</td>
</tr>
<tr>
<td>Afro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High HIV</td>
<td>26.7</td>
<td>7.05</td>
<td>64.4</td>
<td>3.1</td>
<td>3.12</td>
</tr>
<tr>
<td>Low HIV</td>
<td>1.28</td>
<td>24.7</td>
<td>4.14</td>
<td>8.0</td>
<td>12.1</td>
</tr>
</tbody>
</table>

RR – relative risk; PAF – population attributable risk

1 – Cresswell, Eur Respir J, 2011
TB outcomes in DM patients
Systematic Review of 33 studies

Take home message
• Trend toward delayed conversion
• Increased risk of relapse, RR 3.89 (95% CI 2.43-6.23)
• Increased risk of death, RR 1.89 (95% CI 1.52-2.36)

Baker, BMC Medicine, 2011
Diabetes, HIV and risk of TB
Implications

**HIV/DM care**
Enhanced screening in HIV/DM patients
?IPT for all HIV/DM patients not yet on HAART
?Extended TB treatment – how long?

**TB care**
Increased screening for DM among TB patients
Tight glycemic control during ATT
‘Unresolved issues’

• Burden of disease?
• Optimal strategies for integration?
• Capacity Building?

Summary

- Diabetes and abnormalities of glucose metabolism are increasing
- Factors related to rising prevalence include ARV therapy and host factors
- Early detection and prevention of DM and metabolic sequelae of HIV infection need to be public health priorities
Thank You

Acknowledgements

Doreen Ramogola-Masire
Harvey Friedman
Michelle Haas
Robert Gross
Billy Tsim
Raina Philips
Todd Brown
Extra slides
Lipid Effects of Switching Thymidine Analogues to ABC or TDF (RAVE)

Phase IV, open-label, multicenter, randomized, 48-week trial of switching from a thymidine analogue to TDF (n = 52) or ABC (n = 53).

**Take Home Message:** Switching to TDF associated with significant improvements in lipid profiles

*P* values between arm differences.

Fasting glucose
(at HIV diagnosis, antiretroviral therapy initiation, and annually thereafter)

- **< 5.5 mmol/L**
  - Repeat fasting glucose in 1 year

- **5.6-7.0 mmol/L**
  - 2-hr OGTT
  - **< 7.0 mmol/L**
    - IFG alone
      - Lifestyle modifications
    - **7.1-11.0 mmol/L**
      - IFG/IGT
      - Lifestyle modifications
    - **≥ 11.1 mmol/L**
      - DM

- **≥ 7.0 mmol/L**
  - Repeat FG ≥7.0mmol/l?
    - No
    - Yes
      - Lifestyle modifications, metformin or pioglitazone

**Notes:**
- Lifestyle modifications
- Consider metformin with other RFs
- Consider pioglitazone with lipoatrophy
Diabetes 2030 projections
Sub Saharan Africa

Wild, Diabetes Care, 2004
Risk Factors – Age

Increasing age = longer duration of HIV
Increasing age = exposure to older ARVs & > lipodystrophy

Implications:
Estimated 3 million Africans with HIV > 50 years
In RSA approx 20% of all HIV infected persons are > 50 years

HAART
Indirect - Body Partitioning

• **Lipodystrophy Case Definition Study:**¹
  - DM 7% with Lipodystrophy
  - DM 3% without Lipodystrophy

• **D:A:D study:**²
  - Lipohypertrophy
    • HR 1.36 (95% CI 1.09-1.68)

• **ANSR-CO8 Cohort:**³
  - Lipoatrophy
    • HR 2.14 (95% CI 1.3-3.44)

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**Drug specific or all Drugs?**

Thymidine Analogues⁴,⁵
- d4T – biggest culprit

NNRTIs
- ACTG 514² – EFV associated with >30% fat loss

PIs
- ACTG 384⁷ – Nelfinavir associated with 13% fat loss on DEXA

**Conclusions?**
Indirect effect of all drugs
Direct effect of some drugs

Metformin: Adverse Effects

Safe!
Recommended as first line for DM by SEMDSA

- Nausea, vomiting, diarrhea
  - Seen in up to 50% of patients
  - Minimized by slow titration and administration with food

- Lactic acidosis
  - Contraindications
    - Renal insufficiency (Cr >132 $\mu$mol/L in men, > 123 $\mu$mol/L in women)
    - Class III and IV congestive heart failure
    - Hepatic failure
    - Potential for lactic acidosis with antiretrovirals

- May worsen lipoatrophy

Direct Effect
Measuring Insulin Resistance

Gold standard
- Hyperinsulinemic euglycemic clamp
- Insulin suppression test
- Insulin tolerance test

Fasting markers of insulin resistance
- HOMA-IR = FPG (mmol/L)*FPI (µU/mL)/22.5
- QUICKI = 1/[log(FPG) + log(FPI)]
- Bennets S₁
- McCauley

Markers of insulin resistance from OGTT
- Insulin area under the curve
- Insulin sensitivity index (Matsuda)
- Stumvoll ISI_{ogtt}
- Belfiore’s ISI
Problems With Measuring Insulin Resistance

• Gold standard techniques too cumbersome to use clinically
• Insulin resistance markers
  – Useful in populations, not in individual patients
  – Insulin assays not standardized and highly variable
  – No established cutoff points
  – Expensive and difficult to perform
Diabetes - Prevalence 1998-2008
199 Countries¹

Change in age-standardized mean FPG (mmol/l per decade)

Danaei et al, Lancet 2011
Management of DM/IR in HIV patients

**Lifestyle Modification**
- Poor diet & Sedentary
- BMI > 25 (kg/m²) +/- 5kg wt gain
- Men > 94 cm
  - Women > 80 cm

**Blood Pressure**
- sBP > 140 +/- dBP > 90

**Fasting Blood Sugar**
- Prediabetes: 5.6-6.9 mmol/l
- Diabetes: > 7.0 mmol/l

**Fasting Blood Lipids**
- Tchol > 6.5 mmol/l
  - If DM, Tchol > 5.0 mmol/l

**Structured Nutritional Counselling & Lifestyle Modification**
- Goal directed counseling
  - Improve diet
  - Smoking Cessation
  - Daily Exercise

**Medical Management**
- Anti HTN meds
  - Goal directed
- Prediabetes – lifestyle +/- metformin
  - Diabetes: Goal directed
- Tchol ↑
  - Consider statin
  - Triglycerides ↑
  - Consider fibrate
Screening & Diagnosis  
Glycated Hemoglobin & HIV

• HbA1c - Underestimates plasma glucose levels in HIV infected patients by 10-15%\(^1\)
  – Discordance associated with NRTI-related macrocytosis\(^2\)
  – Abacavir: increased discordance\(^2\)

• SEMDSA\(^3\) & ADA\(^4\): HbA1c –for monitoring, not DM diagnosis

Effects of Antiretroviral Therapy on Lipids

- **LDL**: tends to go up modestly with virtually all regimens

- **PIs**: Major effect of most boosted PI regimens is increased TG and non–HDL-C, but HDL-C typically increases as well

- **NNRTIs**: Increase HDL-C; also increase in LDL-C and TG with EFV

- **NRTIs**: d4T and ZDV associated with adverse effects on lipids relative to TDF (and ABC)

- **New classes**: MVC and RAL do not appear to adversely affect lipids
Randomized Trial of Lipid-Lowering Therapy vs Switching PI

Take Home Message: Statin more effective in management of hyperlipidemia than switching antiretroviral therapy to an NNRTI

BUT

Lipid drugs have side effects… Only if virologic suppression can be assured is switch reasonable.

Statins in HIV

Best evidence for CVD reduction and long-term safety

- **Lipid effects**
  - ↓↓↓ LDL-C, non–HDL-C
  - ↓↓ TG, ↑↑ HDL-C

- **Potency varies by agent**
- **Major adverse effects are dose dependent**
  - Myalgia/myopathy
  - Abnormal liver function tests

- **Monitoring**
  - Transaminases at BL, 6-8 weeks, then yearly
  - CK only if muscle symptoms

**Alert!**
Potential interactions with PIs/NNRTIs

**NNRTI** – ↓ levels of statins between 40-80%

**PIs** – ↑ levels of statins to supratherapeutic levels

Simvastatin AUC ↑ 505% with NFV; ↑ 3059% with SQV/RTV
Atorvastatin AUC ↑ 588% to 900% with LPV/RTV
Lipid-Lowering Agents and PIs: Drug-Drug Interactions

- Fibrates
  - Fluvastatin
  - Pravastatin*
  - Ezetimibe
  - Fish oil

- Statin + Fibrate
  - Atorvastatin
  - Rosuvastatin
  - Niacin

- Lovastatin
- Simvastatin

**Contraindicated**

**Use cautiously**

**Low interaction potential**
NNRTI Drug Interactions With Statins

• **EFV**: mixed inducer/inhibitor of CYP450 3A4
  - Simvastatin AUC ↓ 58%
  - Atorvastatin AUC ↓ 43%
  - Pravastatin AUC ↓ 40%

• **NVP**: inducer of CYP450 3A4
  - Not studied with lipid-lowering therapy
  - Probably the same as EFV
Statins: ALLRT study

• HIV infected individuals on HAART, randomized to receive statin, regardless of LDL or total Cholesterol (n=3601)

Statin use-

• Non-significant ↓ decrease in non-AIDS events or death, HR: 0.81 (95% CI: 0.58-1.35)
• Significant ↓ in risk of non-AIDS cancer, HR: 0.43 (95% CI: 0.19-0.94)

1. Overton, CROI, 2012