Metabolic Syndrome and Diabetes Mellitus in Treated HIV Infection

Jordan E. Lake, MD, MSc
Associate Professor
University of Texas Health Science Center at Houston
Learning Objectives

Upon completion of this presentation, learners should be better able to:

– Explain how diabetes and metabolic syndrome differ in persons living with HIV (PLWH) compared to those without HIV
– Assess risk for diabetes and metabolic syndrome in PLWH
– Summarize important considerations for managing PWLH and diabetes and/or metabolic syndrome
Faculty and Planning Committee Disclosures

Please consult your program book.

• Consultant for Gilead Sciences and Merck.
• Research support from Gilead Sciences.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Case

- 53 year-old African American male, HIV+ for 20 years, on antiretroviral therapy (ART) since 2000
- VL< 50 copies/mL on FTC/TDF/EFV
- Mild/moderate lipoatrophy of face/buttocks/thighs
- Mild HTN, normal lipids, no smoking
- Strong family history of diabetes mellitus (DM)
- BMI 27 kg/m² with increased waist circumference
How many DM risk factors does he have?

- 53 year-old
- African American Male,
- HIV+ for 20 years,
- On FTC/TDF/EFV
- Mild/moderate lipoatrophy
- Mild HTN, normal lipids, no smoking
- Strong family history of DM
- BMI 27 kg/m² with increased waist circumference

a. 1  
b. 2  
c. 3  
d. 4  
e. >4
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/sp-isq7fv

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Epidemiology of Diabetes in PLWH

- Prevalence estimates vary from 2-14%, dependent upon cohort characteristics and how DM is defined (general population about 9%)

- Research also conflicting as to whether HIV is an independent risk factor for DM *per se*, but, at a minimum, convergence of traditional (age, obesity, genetics) and HIV-/ART-specific risk factors seems to heighten risk

Pathogenesis of Diabetes in People Living With HIV

• ART Factors
  – Thymidine analogues, older protease inhibitors (PIs), efavirenz
  – Less dramatic effects with modern ART

• HIV Factors
  – Persistent immune activation/inflammation cause systemic disruption of tissue function
  – Gut barrier breach ➔ circulating bacterial products ➔ insulin resistance and lipolysis
  – May be exacerbated in obesity

Circulating Lipopolysaccharide (LPS) Levels Correlate with Insulin Resistance and Dyslipidemia in HIV

Pedro et al, Diabetol Metab Syndr, 2018
Pathogenesis of Diabetes in PLWH

- Host Factors
  - Generalized obesity, peripheral lipoatrophy and central lipohypertrophy
  - HCV co-infection
  - Family History, Race/ethnicity
  - Hypogonadism
  - Concomitant Medications: corticosteroids, atypical antipsychotics, statins
    (benefit of latter thought to outweigh risk*)

Monroe et al, CID, 2014
*Expert/personal opinion
Diagnosis of Diabetes in PWLH

"I have your test results. Your sugar is too high."
Case: How should we screen our 53 yo HIV+ male patient for diabetes?

a. Fasting plasma glucose
b. Oral glucose tolerance testing
c. HbA1c
d. a or b
e. All of the above
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/spfk09n7

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
ADA DM Screening Recommendations for US Gen Pop

Age 45 or overweight or obese adults with one or more of the following:

- Previous pre-diabetes
- 1st degree relative with DM
- High-risk race/ethnicity
- Women with h/o gestational diabetes mellitus or Polycystic Ovarian Syndrome
- H/o cardiovascular disease
- Hypertension (BP >140/90 mmHg or on therapy)
- HDL cholesterol <35 mg/dL or triglycerides >250 mg/dL
- Physical inactivity
- Other conditions associated with insulin resistance

http://care.diabetesjournals.org/content/41/Supplement_1
Diabetes Screening Recommendations: PWLH

Who:
- every 6-12 months prior to ART initiation
- within 3 month weeks after ART initiation or switch
- every 6-12 months thereafter

How: ADA 2018 gen pop guidelines
- A1C ≥6.5%
- Fasting plasma glucose ≥ 126 mg/dL, confirmed by repeat testing
- Plasma glucose 2 hours after 75 g oral glucose tolerance test ≥ 200 mg/dL
- Random plasma glucose ≥ 200 mg/dL with symptoms of hyperglycemia

http://care.diabetesjournals.org/content/41/Supplement_1
Caveat About HbA1c in HIV

“For conditions with abnormal red cell turnover......, the diagnosis of diabetes must employ glucose criteria exclusively”

http://care.diabetesjournals.org/content/41/Supplement_1
HbA1c Underestimates Glycemia in PWLH

Kim et al, *Diabetes Care*, 2009

Slama et al, *JAC*, 2014
Diabetes Screening in PLWH

- **How (revised):**
  - Fasting Glucose
  - If 100-125 mg/dL, consider 75g OGTT
  - Avoid A1c for screening (particularly in those on ABC, low CD4+ T cell count, PIs, high MCV)

http://care.diabetesjournals.org/content/41/Supplement_1
Treatment of Diabetes

- Lifestyle Modification

“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
Lifestyle Modification

- Moderate intensity aerobic exercise *plus* nutritional optimization recommended for all

- Calorie guideline options for weight loss
  1. 1200–1500 calories/day for women or 1500–1800 calories/day for men
  2. An energy deficit of 500-750 calories per day
  3. An evidence-based diet that restricts a certain food type (e.g., high-carbohydrate foods) to create an energy deficit.

- Target ≥5-7% weight loss

Effect of Cutting 500 kcal/day in Obese Persons

Effect on Weight

Effect on Inflammation

Hermana et al, *Endocrine*, 2009
Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association

Diabetes Care 2016;39:2065–2079 | DOI: 10.2337/dc16-1728

Prolonged sitting should be interrupted with bouts of light activity every 30 min for blood glucose benefits, at least in adults with type 2 diabetes.
Diabetes Prevention

Diabetes Prevention Program:
• 150 minutes/week of exercise and caloric restriction for ≥7% weight loss
• ↓ 58% diabetes incidence

In HIV, similar recommendations as general population, plus optimize ART

Knowler et al, NEJM, 2002
After DM is diagnosed, what should be the next steps?

- Lifestyle Modification
- First-line Drug
- Combination Therapy
Case: 53 yo AAM fails lifestyle modification attempt, what is next steps?

a. Refer him to endocrine
b. Metformin
c. Insulin
d. Sulfonylurea
e. All of the above
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/sp-xcby9b

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
More About Metformin

**Pros**
- ↓ A1c ~1%
- Long track record of use
- No hypoglycemia
- No weight gain
- ? CVD benefit
- Low cost

**Cons**
- Interaction with DTG
- GI side effects
- Lactic acidosis (rare)
- Contraindications:
  - CKD (Okay if eGFR > 30 cc/min/1.73 m²)
  - Hypoxia
  - Decompensated Liver Disease
  - Severe CHF
  - Alcohol Abuse
  - Past H/O Lactic Acidosis
What About Second Line Therapy?

- Lifestyle Modification
- First-line Drug
- Combination Therapy
What drug to add for combination therapy?

- Sulfonylureas (glipizide) stimulate insulin secretion from pancreas
- Glitazones (pioglitazone) = PPAR-γ agonists, increase glucose oxidation
- Insulin
- SGLT-2 Inhibitors
- GLP-1 Analogues
- DPP-IV Inhibitors

Incretins = stimulate insulin release and block glucagon release
Sulfonylureas: Pros and Cons

**Pros**
- ↓ A1c ~1%
- Long track record
- ↓ microvascular events
- Low cost
- **Good in patients with food insecurity** as can be taken at time of meal/short-acting

**Cons**
- Weight gain
- Hypoglycemia
- High failure rate
## Pioglitazone: Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ A1c ~1%</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• No hypoglycemia</td>
<td>• Fluid retention/CHF</td>
</tr>
<tr>
<td>• ? CVD benefit</td>
<td>• Macular edema</td>
</tr>
<tr>
<td>• ↑ HDL, ↓ TGs</td>
<td>• Osteoporosis/fracture risk</td>
</tr>
<tr>
<td>• ↓ Liver fat</td>
<td>• Bladder cancer</td>
</tr>
<tr>
<td>• ? ↓ Inflammation</td>
<td>• Cost</td>
</tr>
<tr>
<td>• Low failure rate</td>
<td></td>
</tr>
<tr>
<td>• Modest effect on lipoatrophy (~+200-500 g)</td>
<td></td>
</tr>
</tbody>
</table>
Insulin: Pros and Cons

Pros

• ↓ A1c: unlimited
• ↓ Microvascular events

Cons

• Hypoglycemia
• Home glucose monitoring
• Weight gain
• Injectable
• Cost

Recommended as/with first line if HbA1c ≥10%/fasting glucose ≥300 mg/dL, severe liver disease/kidney disease, hypertriglyceridemia, symptomatic hyperglycemia

http://care.diabetesjournals.org/content/41/Supplement_1
Sodium Glucose Co-transporter 2 Inhibition: The “gliflozins”

Pros
- Insulin-independent reduction in glucose
- ↓ CVD risk
- 0.5-1% A1c reductions
- Weight loss (∼2kg)
- Lowers BP
- No hypoglycemia

Cons
- ↑ urinary tract infections/candidiasis
- Polyuria/dehydration
- ↑ DKA risk
- ↑ Bony fractures
- High cost
Empagliflozin Reduced CVD Events in DM Patients with High CVD Risk

A Primary Outcome

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P = 0.04 for superiority

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>4687</td>
<td>4580</td>
</tr>
<tr>
<td>6 months</td>
<td>4455</td>
<td>4258</td>
</tr>
<tr>
<td>12 months</td>
<td>4328</td>
<td>4112</td>
</tr>
<tr>
<td>18 months</td>
<td>3851</td>
<td>3875</td>
</tr>
<tr>
<td>24 months</td>
<td>2821</td>
<td>2738</td>
</tr>
<tr>
<td>30 months</td>
<td>2359</td>
<td>2351</td>
</tr>
<tr>
<td>36 months</td>
<td>1534</td>
<td>1491</td>
</tr>
<tr>
<td>42 months</td>
<td>370</td>
<td>350</td>
</tr>
</tbody>
</table>

Zinman et al, NEJM, 2015
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion of food

Beta cells: Enhances glucose-dependent insulin secretion

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Adapted from Flint et al, J Clin Invest, 1998; Adapted from Larsson et al, Acta Physiol Scand, 1997; Adapted from Nauck et al, Diabetologia. 1996; Adapted from Drucker, Diabetes, 1998.
DPP-IV Inhibitors: Pros and Cons

Pros
• No hypoglycemia
• Weight neutral
• ? ↓ Inflammation

Cons
• ↓ A1c ~0.5%
• GI Side Effects
• ?Pancreatitis
• Hypersensitivity reaction
• No CVD benefit
• Heart failure
• Cost
### GLP-1 Analogues/Receptor Agonists: Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ A1c ~1%</td>
<td>• GI side effects</td>
</tr>
<tr>
<td>• No hypoglycemia</td>
<td>• ? ↑ pancreatitis</td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Cost</td>
</tr>
<tr>
<td>• ? ↓ Inflammation</td>
<td></td>
</tr>
</tbody>
</table>
Liraglutide Decreases CVD Events in High Risk Type 2 DM Patients: The LEADER Trial

Marso et al, NEJM, 2016
Liraglutide Reduces Visceral and Subcutaneous Fat in Pre-DM and Early DM

Santilli et al, Diabetes Care, 2017
Liraglutide Reduces HbA1c and 2-hour Post-Prandial Glucose in Pre-DM and Early DM

Santilli et al, *Diabetes Care*, 2017
Anti-hyperglycemic therapy in Type 2 DM: General Recommendations

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td><strong>Hypo risk</strong></td>
<td><strong>Hypo risk</strong></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td><strong>Weight</strong></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td><strong>Side effects</strong></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td><strong>Costs</strong></td>
</tr>
</tbody>
</table>

**Healthy eating, weight control, increased physical activity, and diabetes education**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Monotherapy</th>
<th>Dual therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
<td>high</td>
<td>Metformin</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>neutral / loss</td>
<td>moderate risk</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Therapy</th>
<th><strong>Sulfonylurea</strong></th>
<th><strong>Thiazolidinedione</strong></th>
<th><strong>DPP-4 inhibitor</strong></th>
<th><strong>SGLT2 inhibitor</strong></th>
<th><strong>GLP-1 receptor agonist</strong></th>
<th><strong>Insulin (basal)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td><strong>Hypo risk</strong></td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>gain</td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>high</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>hypoglycemia</td>
<td>edema, HF, fx</td>
<td>edema, HF, fx</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>gain</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>

©2015 by American Diabetes Association

Inzucchi et al. *Diabetes Care*, 2015
ADA Recommendations 2018

“In patients with established CVD, anti-hyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide).”

http://care.diabetesjournals.org/content/41/Supplement_1
ADA Recommendations 2018

“In patients with established CVD, anti-hyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide).”

So maybe for all HIV-infected persons with DM?

http://care.diabetesjournals.org/content/41/Supplement_1
A1c Goal

General: HbA1c < 7%

Individualization is Key:
• Tighter Control (A1c 6.0-6.5%): Younger, Healthier
• Looser Control (A1c 7.5-8.0%+): Older, Hypoglycemia Prone, Some Comorbidities

Where does HIV fit in?
Preventing microvascular complications:

- **Retinopathy**: Yearly ophthalmologic exams
- **Nephropathy**:
  - BP, glucose, lipid control
  - Spot urine microalbumin every 6-12 months
  - ACEi/ARB if microalbuminuria, HTN, eGFR <60 mL/min
  - Protein intake 0.8g/kg/day if CKD but not on dialysis
- **Neuropathy**:
  - Foot exams annually starting at diagnosis
  - Instruction in home foot care
  - Podiatry if loss protective response, PVD, prior DM foot complications

http://care.diabetesjournals.org/content/41/Supplement_1
Preventing macrovascular complications:

Attention to all CVD risk factors
- Anti-platelet therapy
- Blood pressure
- Cholesterol
- Diabetes/Glucose Management
- Smoking Cessation

Steno-2 Trial (Gaede, NEJM, 2003): CVD Events ↓ by 50% with intensive control of all CVD Risk Factors

http://care.diabetesjournals.org/content/41/Supplement_1
Conclusions

• Regular DM screening is important, and indicated for all PWLH
• Avoid HbA1c for diagnosis in HIV
• Lifestyle changes are critical. Goal is 5-7% weight loss
• Metformin first
• Decisions re: 2\textsuperscript{nd} and 3\textsuperscript{rd} drugs should be individualized
• A1c goal < 7% in most, but should be individualized
• Multi-prong approach to prevent complications
Acknowledgements

• Todd Brown for assistance with slides/content
What drug to add next?

Cost Recap (AWP/month)
- Glipizide ($75)
- Metformin (IR $87, ER $1028)
- Insulin ($200-$400)
- Pioglitazone ($348)
- Sitagliptin ($477)
- Empagliflozin ($517)
- Liraglutide ($968)

http://care.diabetesjournals.org/content/41/Supplement_1
Medical Expenditure Panel Survey

Figure. Mean Expenditure per Patient for Antihyperglycemic Medications, 2002-2013

Hua et al, JAMA, 2016