Diabetes Risk Assessment and Treatment

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Disclosures

• Consultant: Gilead Sciences, Merck, BMS, EMD-Serono, Theratechnologies
Learning Objectives

– Explain how diabetes differs in persons with HIV infection compared to those without HIV
– Recommend how persons with HIV infection should be assessed for diabetes risk
– Summarize important considerations for managing patients with HIV infection and diabetes
Why Care about Diabetes?

• Very common, with rapidly increasing prevalence
• One of leading causes of cardiovascular disease, blindness, ESRD, amputations, hospitalizations
• Common in HIV-infected populations
• Diabetes can be controlled, but management is complicated and requires individualization
THE STAGGERING COSTS OF DIABETES IN AMERICA

Nearly
30 million
Americans have diabetes.

$1 in $3
Medicare dollars is spent caring for people with diabetes.

$322 billion
per year.

Diabetes and prediabetes cost America

Today,
3,835
Americans will be diagnosed with diabetes. Today, diabetes will cause
200 Americans to undergo an amputation, 136 to enter end-stage kidney disease
treatment and 1,795 to develop severe retinopathy that can lead to vision loss and blindness.

86 million
Americans have prediabetes.

$1 in $5
health care dollars is spent caring for people with diabetes.

Learn how to fight this costly disease at diabetes.org/congress
Pathogenesis of Diabetes in HIV-infected Patients

- **Antiretroviral Medication Factors**
  - Thymidine analogues, older PIs
- **HIV Factors**
  - Residual immune activation/inflammation
- **Host Factors**
  - Adiposity
  - HCV
  - Genetic factors: family history, race
  - Coadministered medications: corticosteroids/atypical antipsychotics
Case

- 53-year-old African American male, HIV+ for 20 years, on ART since 2000
- VL<50 FTC/TDF/ EFV
- Mild/moderate lipoatrophy of face/buttocks/thighs
- Mild HTN, normal lipids, no smoking
- Strong family history of DM
- BMI 27 kg/m²
ADA Screening Guidelines in General Population

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 GDM
- H/O CVD
- HTN
- Low HDL or high TG
- Women with polycystic ovarian syndrome
- Physical inactivity
- Other conditions associated with IR
Diabetes Screening Guidelines for HIV-infected Persons

• Who?
  – IDSA: Prior to ART, within 4-6 weeks after ART initiation, every 6-12 months thereafter
How?: ADA Definitions 2017

Diabetes Mellitus

1. A1C $\geq 6.5\%$

2. Fasting plasma glucose $\geq 126$ mg/dL, confirmed by repeat testing

3. Plasma glucose 2 hours after 75 g oral glucose tolerance test $\geq 200$ mg/dL

4. Random plasma glucose $\geq 200$ mg/dL with polyuria and polydipsia

#1-3 should be confirmed on repeat testing
Caveats for the Use of HgbA1c for Diagnosis

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

ADA Clinical Practice Recommendations, 2017
HbA1c Underestimates Glycemia in HIV-infected Persons

Kim, Diabetes Care, 2009

- HIV (n=100)
- Control (n=200)
Diabetes Screening in HIV-infected Persons

• How?
  – Fasting glucose
  – If 100-125 mg/dL, consider 75 g OGTT
  – Avoid A1c for screening (particularly in those on ABC, low CD4, PIs, high MCV)
Case

- 53-year-old African American male, HIV+ for 20 years, on ART since 2000
- VL< 50 FTC/TDF/ EFV
- Mild/moderate lipoatrophy of face/buttocks/thighs
- Mild HTN, normal lipids, no smoking
- Strong family history of DM
- BMI 27 kg/m²
- Fasting glucose 145 mg/dL (confirmed)
- A1c 6.8%
After DM Is Diagnosed, What Should Be the Next Steps?

• Lifestyle modification
• First-line drug
• Combination therapy
Lifestyle Modifications for Prediabetes

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

Effect of Cutting 500 cal/day over 8 weeks in Obese Persons

Effect on Weight

Effect on Inflammation

Hermana, 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
Benefits of and Recommendations for Reduced Sedentary Time

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.
After DM Is Diagnosed, What Should Be the Next Steps?

- Lifestyle modification
- First-line drug
- Combination therapy
Metformin: THE First Line Drug
Metformin: Pros and Cons

**Pros**
- \( \downarrow \text{A1c} \sim 1\% \)
- Long track record
- No hypoglycemia
- No weight gain
- ? CVD benefit
- Low cost (AWP $86/month)

**Cons**
- GI side effects
- Lactic acidosis (rare)
- Contraindications:
  - CKD (OK eGFR >30 cc/min/1.73 m\(^2\))
  - Hypoxia
  - Decompensated liver disease
  - Severe CHF
  - Alcohol abuse
  - Past H/O lactic acidosis
- ? Worsening lipoatrophy
- Interaction with DTG
After DM Is Diagnosed, What Should Be the Next Steps?

- Lifestyle modification
- First-line drug
- Combination therapy
What Drug to Add Next?

- Sulfonylureas
- Glitazones (pioglitazone)
- Insulin
- GLP-1 analogues
- DPP-IV inhibitors
- SGLT-2 inhibitors

Incretins
Sulfonylureas: Pros and Cons

Pros
• ↓ A1c ~1%
• Long track record
• ↓ Microvascular events
• Low cost (AWP $74/month)

Cons
• Weight gain
• Hypoglycemia
• High failure rate
Pioglitazone: Pros and Cons

Pros

- \( \downarrow \) A1c ~1%
- No hypoglycemia
- ? CVD benefit
- \( \uparrow \) HDL, \( \downarrow \) TGs
- \( \downarrow \) Liver fat
- ? \( \downarrow \) Inflammation
- Low failure rate
- Modest effect on lipoatrophy (~200-500 g)

Cons

- Weight gain
- Fluid retention/CHF
- Macular edema
- Osteoporosis/fracture
- Bladder cancer
- Cost (AWP $349/month)
Insulin: Pros and Cons

**Pros**
- ↓ A1c: unlimited
- ↓ Microvascular events

**Cons**
- Hypoglycemia
- Weight gain
- Injectable
- Cost (insulin glargine AWP $298/month; NPH vial AWP $165/month)
Starting Insulin in Type 2 DM

• Start with bedtime glargine, detemir, or NPH (10 units, increase by 2-3 units q 3 days until fasting is <120 mg/dl)

• Add prandial insulin (10% of basal dose before largest meal), GLP-1 analogue, or switch to 70/30 bid if not at goal

• Recommended as first line if A1c ≥10%, severe liver disease/kidney disease, hypertriglycerideridemia
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Beta cells:
Enhances glucose-dependent insulin secretion

Alpha cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

### Incretins

<table>
<thead>
<tr>
<th>GLP-1 Analogues</th>
<th>DPP-IV Inhibitors</th>
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<tr>
<td>Exenatide</td>
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GLP-1 Analogues: Pros and Cons

Pros
- ↓ A1c ~1%
- No hypoglycemia
- Weight loss
- ? ↓ Inflammation
- CVD benefit

Cons
- GI side effects
- ? ↑ pancreatitis
- Cost (AWP $831/month)
Liraglutide Decreases CVD Events in High-Risk Type 2 Patients: LEADER Trial

Marso, NEJM, 2016
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 (AWP $436/month)
Sodium Glucose Cotransporter-2 Inhibition: The “Gliflozins”

- Insulin-independent reduction in glucose
  - dapaglifozin
  - canagliflozin
  - empagliflozin
- 0.5%-1% A1c reductions
- Weight loss (~2kg)
- Lowers BP
- No hypoglycemia
- ↑ urinary tract infections/candidiasis
- Polyuria/dehydration
- ↑ DKA risk
- ↑ Bone fractures
- High cost (AWP $470/month)
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

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Zinman, NEJM, 2015
What Drug to Add Next?

- Sulfonylureas
- Glitazones (pioglitazone)
- Insulin
- GLP-1 analogues
- DPP-IV inhibitors
- SGLT-2 inhibitors

Incretins
Cost vs. Benefits vs. Risks
What Drug to Add Next?

- Sulfonylureas
- Glitazones (pioglitazone)
- Insulin
- GLP-1 analogues
- DPP-IV inhibitors
- SGLT-2 inhibitors

Incretins
“Consider empagliflozin or liraglutide in patients with established CVD to reduce the risk of mortality.”
What Should Be the Glycemic Target?

HbA1c < 7%
Meta-Analysis of Glycemic Control and CVD in Diabetes

10% Risk Reduction for CVD

No Benefit on CVD Mortality

2-fold increase risk of severe hypoglycemia with intensive control

A1c Goal

HbA1c <7%

Individualization Is Key:
• Tighter control (A1c 6.0-6.5%): younger, healthier
• Looser control (A1c 7.5-8.0%+): older, hypoglycemia-prone, comorbidities
What Else Should I Be Doing to Prevent Complications?: Microvascular

- Retinopathy: yearly ophthalmologic exams
- Nephropathy:
  - BP control
  - Spot urine microalbumin every 6-12 months
  - ACE-I/ARB with microalbuminuria or HTN
  - Lipid control
- Neuropathy:
  - Foot exams every 6-12 months
  - Instruction in foot care
  - Podiatry if evidence of neuropathy
What Else Should I Be Doing to Prevent Complications?: Macrovascular

- Attention to all CV risk factors
  - A: Antiplatelet therapy
  - B: Blood pressure
  - C: Cholesterol
  - D: Diabetes/glucose management
  - S: Smoking cessation

Steno-2 Trial (Gaede, NEJM, 2003): CV events ↓ by 50% with intensive control of all CV risk factors
Conclusions

• Regular DM screening is important
• Avoid A1c for diagnosis in HIV+ patients
• Lifestyle changes are critical
  – 5%-10% wt loss!
• Metformin first
• Decisions re: 2nd and 3rd drugs should be individualized
• A1c goal <7% in most, but should be individualized
• Multiprong approach to prevent complications