Managing Diabetes Mellitus in the HIV-infected Patient

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Disclosures
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Off-Label Disclosure
There will be no off-label/investigational uses discussed in this presentation

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
Pathogenesis of Diabetes in HIV-infected Patients

- Antiretroviral Medication Factors
  - Thymidine analogues, older PIs
- HIV Factors
  - Residual immune activation/inflammation
- Host Factors
  - Adiposity (INSTI-related?)
  - HCV
  - Genetic Factors: Family History, Race
  - Concomitant Medications: Corticosteroids/Aтипical Antipsychotics

Diabetes Screening Guidelines for HIV-infected Persons

- Who?
  IDSA: Prior to ART, within 4-6 weeks after ART initiation, every 6-12 months thereafter

Aberg, CID, 2013
Case

• 53 year-old African American Male, HIV+ for 20 years, on ART since 2000
• VL < 50 FTC/TAF/DTG
• Mild/moderate lipoatrophy of face/buttocks/thighs
• Mild HTN, Normal lipids, no smoking
• Strong family history of DM
• BMI 27 kg/m²
• A1c 6.2%

Case

Does this patient have diabetes?
1. Yes
2. No
3. Can’t tell
How?: ADA Definitions

Diabetes Mellitus

1. A1C ≥6.5%
2. Fasting plasma glucose ≥ 126 mg/dL, confirmed by repeat testing
3. Plasma glucose 2 hours after 75 g oral glucose tolerance test ≥ 200 mg/dL
4. Random plasma glucose ≥ 200 mg/dL with polyuria and polydipsia

#1-3 should be confirmed on repeat testing

Caveats for the use of HgbA1c for diagnosis

"In conditions associated with an altered relationship between A1C and glycemia, such as sickle cell disease… HIV….only plasma blood glucose criteria should be used to diagnose diabetes.”

Standards in Medical Care in Diabetes, Diabetes Care, 2019
HbA1c Underestimates Glycemia in HIV-infected Persons

![Graph showing glucose levels vs. HbA1c (%) for HIV-infected and control groups.](image)

Kim, Diabetes Care, 2009

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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)

Author’s Opinion; Slama, JAC, 2014
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:

Hermana, Endocrine, 2009

Effect on Inflammation:

Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association

Diabetes Care 2016;39:1065-1079 | DOI: 10.2337/dc16-1729
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
• ↓ A1c ~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 m²)
  – Hypoxia
  – Decompensated Liver Disease
  – Severe CHF
  – Alcohol Abuse
  – Past H/O Lactic Acidosis
  –  ? Worsening Lipoatrophy
• Interaction with DTG

Davies, Diabetes Care, 2018; Author’s Opinion

After DM is diagnosed, what should be the next steps?

• Lifestyle Modification
• First-line Drug
• Combination Therapy
Case

• 54 year-old African American Male, HIV+ for 21 years, on ART since 2000
• VL< 50 FTC/TAF/DTG
• Mild/moderate lipoatrophy of face/buttocks/thighs
• On metformin 500 mg bid
• A1c 7.8%

What is the optimal approach to manage his diabetes?

1) No changes to medications needed. Lifestyle modifications reinforced.
2) Increase metformin to 1000 mg bid
3) Add sulfonylurea
4) Add GLP-1 analogue
5) Add pioglitazone
6) Add SGLT2 inhibitor
7) Add DPP-IV inhibitor
8) Add glargine insulin at night
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

Davies, Diabetes Care, 2018; Author’s Opinion
Pioglitazone: Pros and Cons

Pros
- ↓ A1c ~1%
- No Hypoglycemia
- ? CVD benefit
- ↑ HDL, ↓ TGs
- ↓ Liver Fat
- ? ↓ 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)

Davies, Diabetes Care, 2018; Author’s Opinion

Insulin: Pros and Cons

Pros
- ↓ A1c: Unlimited
- ↓ Microvascular events

Cons
- Hypoglycemia
- Weight Gain
- Injectable
- Cost (Lantus AWP $298/month; NPH vial AWP $165/month)

Davies, Diabetes Care, 2018; Author’s Opinion
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, hypertriglyceridemia

Davies, Diabetes Care, 2018; Author’s Opinion

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion food

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

Beta cells: Enhances glucose-dependent insulin secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Incretins

GLP-1 Analogues
- exenatide (Byetta)
- liraglutide (Victoza)
- exenatide LAR (Bydureon)
- dulaglutide (Trulicity)
- albiglutide (Tanzeum)
- lixisenatide (Lyxumia)
- semaglutide (Ozempic)

DPP-IV Inhibitors
- sitagliptin (Januvia)
- saxagliptin (Onglyza)
- vildagliptin (Galvus)
- linagliptin (Trajenta)
- alogliptin (Nesina)

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)

Davies, Diabetes Care, 2018; Author’s Opinion
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)

Davies, Diabetes Care, 2018; Author’s Opinion
Sodium Glucose Co-transporter 2 Inhibition: The “gliflozins”

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

Davies, Diabetes Care, 2018; Author’s Opinion

Empagliflozin Reduced CVD Events in DM Patients with High CVD Risk

Zinman, NEJM, 2015
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."

Davies, Diabetes Care, 2018
**Compelling Need to Minimize Hypoglycemia**

- **DPP-4i**
- **GLP-1 RA**
- **SGLT2i**
- **TZD**

If HbA1c above target:

- **SGLT2i** OR **TZD**

**If HbA1c above target**

Continue with addition of other agents as outlined above.

**If HbA1c above target**

Consider the addition of SU OR basal insulin:
- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia

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**Compelling Need to Minimize Weight Gain or Promote Weight Loss**

**SU**

**TZD**

**If HbA1c above target**

- **GLP-1 RA with good efficacy for weight loss**

**If HbA1c above target**

- **SGLT2i**

**If HbA1c above target**

- **GLP-1 RA with good efficacy for weight loss**

**If HbA1c above target**

- **SGLT2i**

**If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain**

- **DPP-4i** (if not on GLP-1 RA) based on weight neutrality

**If HbA1c not tolerated or contraindicated or patient already on GLP-1 RA cautious addition of:**
- **SU** + **TZD** + Basal insulin

**Cost is a Major Issue**

**SU**

**TZD**

**If HbA1c above target**

**If HbA1c above target**

**If HbA1c above target**

**Insulin therapy basal insulin with lowest acquisition cost**

**Consider DPP-4i or SGLT2i with lowest acquisition cost**
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, Co-morbidities

Standards in Medical Care in Diabetes, Diabetes Care, 2019

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

Author’s Opinion
What else should I be doing to prevent complications?: Macrovascular

- Attention to all CV risk factors
  
  A: Anti-platelet 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: 2\textsuperscript{nd} and 3\textsuperscript{rd} drugs should be individualized. Consider gliptin/gliflozin in those with ASCVD  
- A1c goal < 7% in most, but should be individualized  
- Multiprong approach to prevent complications
BMI Gain After ART Initiation: D:A:D

Achhra, HIV Med, 2016
Risk of DM by Unit Increase in BMI over First Year After ART Initiation

Achhra, HIV Med, 2016

Risk of DM with Weight Gain over 1 Year after ART Initiation

Herrin, JAIDS, 2016

adjusted for age, race, sex, baseline BMI, smoking, HCV infection, and calendar year at baseline
ART Initiation at Parkland Hospital Dallas: INSTI Effect in Women and Non-Whites

Multivariable analysis of yearly BMI changes on HAART (figure 1) was limited to participants with baseline viremia of ≥400 copies/ml (n=3208).

Figure 1: Comparisons of Yearly BMI Changes on HAART by sex (A) and by race/ethnicity (B).

Weight Gain is Greater with INSTI in NA-ACCORD

Lake, 20th IWCADRH, 2018
ACTHIV 2019: A State-of-the-Science Conference for Frontline Health Professionals