Diabetes Medications for Type 2 Diabetes with Focus on HIV: Part 1

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Objectives

• Understand how to safely prescribe and use older diabetes medications

• Understand physiology and mechanism of action, efficacy, safety, tolerability, managing side effects, dosing and administration of individual drugs

• Understand use in setting of HIV

• Assess the cardiac and renal benefits or lack of cardiac benefits in these older medications
Adverse Effects Associated with HIV and Treatment of HIV

- Changes in body composition
- Dyslipidemia
- Insulin resistance
- Type 2 diabetes
- Vascular endothelial dysfunction.
- HIV larger risk for onset of comorbidities than do their HIV-negative peers
- Shorten the life expectancy of people living with HIV

Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.

**FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)**

**INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF**

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE

**+ASCVD/indicators of High Risk**
- Established ASCVD
- Indicators of high ASCVD risk (age ≥ 35 years with coronary, carotid, or lower-extremity artery stenos ≥50%, or LWM)

**+HF**
- Particularly HFpEF (LVEF <45%)

**+CKD**
- Dpd and Albuminuria
- SGLT2i with proven benefit in this population

If A1C above target

**For patients with T2D and CKD (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events**

**PREFERABLY**
- SGLT2i with proven primary evidence of reducing CVD progression in CVOT trials
- OR
- GLP-1 RA with proven CVD benefit

**OR**
- SGLT2i with evidence of reducing CVD progression in CVOT trials
- OR
- GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

If A1C above target

**FOR INDIVIDUALIZED TARGET:**

**If A1C above target**

**COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA**

**COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**

**COST IS A MAJOR ISSUE**

**SU**

**T2D**

**If A1C above target**

**Consider the addition of GLP-1R agonist**
- **SGLT2i**
- **TZD**

**If A1C above target**

**Consider the addition of SU or basal insulin**
- **GLP-1 RA with lower risk of hypoglycemia**
- **T2D**

**If A1C above target**

**If quadruple therapy required, or SGLT2i and GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain or no weight-related complications**

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

**If A1C above target**

**If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of: SGLT2i**
- **SU**
- **TZD**
- **Basal Insulin**

1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Deglucad or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia
5. GLP-1Ra has shown similar CV benefit to DPP-4i
6. Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
7. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HFpEF and to reduce CVD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Deglucad / glargine U-100 = deglucad U-100 / deglucad + NPH insulin
10. Somatostatin = I-arginide + 2-deoxyglucose + vasotec = Inolintex
11. If no specific contraindications (i.e., no established CVD, low risk of hypoglycemia, and prior exposure to weight gain, or no weight-related complications)
12. Consider country- and region-specific cost of drugs. In some countries, TZDs are relatively more expensive and DPP-4i are relatively cheaper.

Abbreviations:
- ADA: American Diabetes Association
- CV: Cardiovascular
- CVOT: Cardiovascular Outcome Trials
- CVD: Cardiovascular Disease
- HF: Heart Failure
- HFpEF: Heart Failure with Preserved Ejection Fraction
- SU: Sulfonylurea
- TZD: Thiazolidinedione
- eGFR: Estimated Glomerular Filtration Rate
- CVOT: Cardiovascular Outcome Trials

*Most patients enrolled in the relevant trials were on metformin at baseline as a glucose-lowering therapy.

> American Diabetes Association Dia Care 2021;44:S111-S124
How to Think about Selecting the Appropriate Diabetes Medication(s)

- Mechanism of action
- Efficacy (on average how much does it lower blood sugar)
- Does it cause hypoglycemia yes/no
- Weight gain/Weight loss/Weight neutral
- Cardiovascular effects
- Use in CKD and renal protective effect
- Use in HIV
- Common side-effects
- Serious side-effects
Clinical benefits of weight loss are progressive and more intensive weight loss goals (i.e., 15%) may be appropriate.

Goal: >7% sustained weight loss

5% is needed to produce beneficial outcomes in glycemic control, lipids, and blood pressure.
Insulin

As glucose toxicity resolves, simplifying the regimen and consider changing to insulin sparing agents if possible

Do not be afraid to use early!

Consider initiating when blood glucose is ≥300 mg/dL (16.7 mmol/L)/A1c >10%
For catabolic features and/or symptoms of hyperglycemia (i.e., polyuria or polydipsia)

Target Sites of Action

Insulin secretion
- ↑ Sulfonyleureas
- ↑ Meglitinides
- ↑ Incretins

Glucagon secretion
- ↓ Incretins
- ↓ Amylin

GI
- Incretins
- α glucosidase inhibitors
- Amylin
- Bile acid sequestrant

Appetite control
- Incretins
- Amylin

Neurotransmitter Dysfunction
- Bromocriptine

Hyperglycemia

Hepatic glucose output
- ↓ Metformin
- ↓ Thiazolidinediones

Lipotoxicity
- Thiazolidinediones

Glucose uptake and utilization
- ↑ Thiazolidinediones
- ↑ Metformin

BIGUANIDES/METFORMIN
### Biguanides/Metformin

<table>
<thead>
<tr>
<th>Class/Main Action</th>
<th>Name(s)</th>
<th>Daily Dose Range</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Biguanides        | metformin (Glucophage)         | 500 - 2500 mg (usually BID w/ meal) | **Side effects:** nausea, bloating, diarrhea, B12 deficiency. To minimize GI Side effects, use XR and take w/ meals. **Obtain GFR before starting.**  
• If GFR <30, do not use.  
• If GFR <45, don’t start Meformin  
• If pt on Metformin and GFR falls to 30-45, eval risk vs. benefit; consider decreasing dose. **For dye study,** if GFR <60, liver disease, alcoholism or heart failure, restart metformin after 48 hours if renal function stable. **Benefits:** lowers cholesterol, no hypo or weight gain, cheap. Approved for pediatrics, 10 yrs + Lowers A1c 1.0%-2.0%. |
|                   | Riomet (liquid metformin)      | 500 - 2500mg 500mg/5mL              |                                                                                  |
|                   | Extended Release-XR (Glucophage XR) (Glumetza) (Fortamet) | (1x daily w/dinner) 500 – 2000 mg 500 – 2000 mg 500 – 2500 mg |                                                                                  |
• Improves insulin sensitivity, it may not be well tolerated by cachexic patients.
• Metformin is more likely to cause diarrhea than other drugs
• Avoided in combination with drugs such as stavudine given risk for Lactic Acidosis
• Abacavir, lamivudine and tenofovir are the least likely drugs to cause elevation of lactate levels
• Metformin was associated with a significant decrease in appendicular fat mass compared with placebo (-686.0 vs 161.0 g; P=0.03). There was no significant change in lipid profile or insulin sensitivity between the two groups at 24 weeks.
# Metformin and HIV

## Interactions with Metformin

<table>
<thead>
<tr>
<th>Antiretroviral (ARV)</th>
<th>Dose of ARV</th>
<th>Dose of Metformin</th>
<th>Effect on ARV Levels</th>
<th>Effect on Metformin Levels</th>
<th>Potential Clinical Effects</th>
<th>Mechanism of Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir&lt;sup&gt;759&lt;/sup&gt; (Biktarvy)</td>
<td>50 mg daily</td>
<td>500 mg twice daily</td>
<td>Not studied</td>
<td>Cmax increased 28%; AUC increased 39%; Cmin increased 36%</td>
<td>Potential increase in metformin adverse effects (gastrointestinal)</td>
<td>-</td>
<td>No dose adjustment necessary; monitor for gastrointestinal adverse effects</td>
</tr>
<tr>
<td>Dolutegravir (Tivicay)</td>
<td>50 mg</td>
<td>500 mg BID</td>
<td>-</td>
<td>Metformin AUC increased 79%; Cmax increase 66%, Cmin increase 9% when given with dolutegravir once daily. If given with dolutegravir 50 mg BID, then metformin AUC increase 2.4 fold; Cmax increase 2 fold and Cmin increase 14%</td>
<td>Potential increased adverse effects from metformin (e.g. GI side effects).</td>
<td>-</td>
<td>In patients taking dolutegravir who are starting metformin, begin with low metformin dose and titrate up carefully. Recommended dose limit of metformin 1000 mg daily. If patient is already on metformin and initiating dolutegravir, monitor glucose, hemoglobin a1c, and metformin adverse effects and adjust dose as necessary.</td>
</tr>
</tbody>
</table>

"..." indicates that there are no data available
Metformin/Risk for Lactic Acidosis

Previous US Food and Drug Administration Prescribing Guidelines for Metformin as Related to Kidney Function

• “Do Not Use”

• Serum creatinine levels:
  - ≥ 1.5 mg/dL males
  - ≥ 1.4 mg/dL females

Source: Metformin final printed labeling
Metformin in Patients With T2D and Kidney Disease: A Systematic Review

Table 2. Possible Approach to Metformin Prescribing in the Setting of CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Maximal Total Dose, mg</th>
<th>Other Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60 -&lt;90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>45 -&lt;60</td>
<td>2000</td>
<td>Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>3B</td>
<td>30 -&lt;45</td>
<td>1000</td>
<td>Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15 -&lt;30</td>
<td>Do not use</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Do not use</td>
<td></td>
</tr>
</tbody>
</table>

Risk for lactic acidosis: 3 per 100 000 person-years to 10 per 100 000 person-years

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

This strategy has not been evaluated or validated in a clinical trial; there are no data to support its efficacy, safety, or potential to improve clinical outcomes.

Metformin: FDA Safety Review of Metformin-Containing Drugs April 2016 updated

UKPDS: CV risk reduction

- The number needed to treat to avoid one death was 14
- ARR 0.07
Liver Disease and Metformin

- 50%-70% reduction in HCC risk among those treated with metformin
- Hep C: reduced in risk for HCC, liver related mortality, and transplantation
- Reduce the incidence of overt hepatic encephalopathy by 8 folds through inhibition of glutaminase activity
- Metformin is often withheld from patients with liver diseases due to an exaggerated concern for metformin-associated lactic acidosis (MALA)
- MALA is an exceedingly rare condition with an estimated incidence of < 10 per 100,000 patient-years of exposure in patients without significant renal impairment
Summary: Metformin

- Try again low dose with Extended release (XR) in those with hx of GI intolerance
- Do not stop if GFR > 30 and can start GFR> 45
- Cheap, low risk hypoglycemia, causes slight weight loss
- May have CV benefits
- Appears to have benefit in Hep C pts and HIV
- Consider decreased dose
- Consider use in prediabetes (hx of GDM, BMI >30, Age <60)
SULFONYLUREAS
Sulfonylureas

- Glimepiride and glipizide associated with a reduced likelihood of hypoglycemia
- Glimepiride also improves first-phase insulin secretion - reducing postprandial hyperglycemia.
- Glyburide more associated with hypoglycemia

| Sulfonylureas | glyburide: (Diabeta) (Glynase PresTabs) | 1.25 – 20 mg  
|              |               | 0.75 – 12 mg |
|              | glipizide: (Glucotrol) (Glucotrol XL)   | 2.5 – 40 mg  
|              |               | 2.5 – 20 mg |
|              | glimepiride (Amaryl)                    | 1.0 – 8 mg   |

- Can take once or twice daily before meals. 
- Low cost generic.
- **Side effects:** hypoglycemia and weight gain. 
- Eliminated via kidney.
- **Caution:** Glyburide most likely to cause hypoglycemia. 
- Lowers A1c 1.0% – 2.0%

https://diabetesed.net/pocket-cards-insulin-and-diabetes-medication/

Diabetes Care 2002 Sep; 25(9): 1607-1611.
Sulfonylureas in CKD

Stage 2 (eGFR 60-90) & Stage 3 (eGFR 59-45):

- Glyburide (Glibenclamide): Limit use in stage 2. Not recommended Stage 3

Stage 4 CKD (eGFR <30)
*Glipizide short acting is preferred (dose 2.5 to 10 mg/day)
Second and Third Generation Sulfonylurea vs. Metformin Monotherapy in Patients with Type 2 Diabetes

B: Cardiovascular mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Events</th>
<th>Control Events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADOPT 2006</td>
<td>8/1447</td>
<td>4/1455</td>
<td>2.01 (0.61–6.66)</td>
</tr>
<tr>
<td>Campbell et al., 1994</td>
<td>0/24</td>
<td>0/24</td>
<td>Not estimable</td>
</tr>
<tr>
<td>DeFronzo et al., 1995</td>
<td>0/209</td>
<td>1/210</td>
<td>0.33 (0.01–8.17)</td>
</tr>
<tr>
<td>Derosa et al., 2004</td>
<td>0/81</td>
<td>0/83</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Hermann et al., 1991b</td>
<td>1/34</td>
<td>0/38</td>
<td>3.34 (0.14–79.42)</td>
</tr>
<tr>
<td>Lawrence et al., 2004</td>
<td>0/22</td>
<td>1/21</td>
<td>0.82 (0.01–7.42)</td>
</tr>
<tr>
<td>Tosi et al., 2003</td>
<td>0/22</td>
<td>0/22</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Yamanouchi et al., 2005</td>
<td>0/37</td>
<td>0/39</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>9/1876</td>
<td>6/1892</td>
<td>1.47 (0.54–4.01)</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C: Nonfatal macrovascular outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Events</th>
<th>Control Events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADOPT 2006</td>
<td>41/1447</td>
<td>58/1455</td>
<td>0.71 (0.48–1.05)</td>
</tr>
<tr>
<td>Hermann et al., 1991b</td>
<td>9/34</td>
<td>18/38</td>
<td>0.56 (0.29–1.07)</td>
</tr>
<tr>
<td>Tosi et al., 2003</td>
<td>0/22</td>
<td>0/22</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Yamanouchi et al., 2005</td>
<td>0/37</td>
<td>0/39</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>50/1540</td>
<td>76/1554</td>
<td>0.67 (0.48–0.93)</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All-cause Mortality: RR 0.98, 95% CI 0.61 to 1.58
Cardiovascular Mortality: RR 1.47, 95% CI 0.54 to 4.01

No increased risk with Sulfonylurea use

Favors Sulfonylurea use
Sulfonylureas and Liver Disease

• Main risk hypoglycemia
• Increased odds of HCC development by up to 3 folds amongst patients with T2DM treated with sulfonylureas
• Expert opinions advise that insulin secretagogues be avoided or used with extreme caution in patients with CLD/ESLD

Chung et al. World J Hepatol 2020 September 27; 12(9): 533-692
Sulfonylureas and HIV

- Insulin secretagogues risk is for hypoglycemia
- The glinides (glimiperide) address the defect in first phase insulin secretion seen in some PI
- Glycemic response was independent of the initial class of diabetic medication prescribed among HIV-uninfected and HIV-infected adults with type 2 diabetes but poorer response among Black and Hispanic patients
Summary: Sulfonylureas

• Continue both metformin and sulfonylureas (glimiperide) if start basal insulin
• Use glimepiride if possible given has more post meal benefit
• Start low dose if eGFR < 60 i.e. 1mg glimepiride
• If eGFR < 30 use glipizide short acting 2.5mg daily to bid
• Weight gain and no CV benefit but also no harm
• Cost effective but may increase risk for hypo and not recommended in those with liver disease

Diabetes Care 2002 Sep; 25(9): 1607-1611.
DIPEPTIDYL PEPTIDASE (DPP)-4 INHIBITORS
Dipeptidyl Peptidase (DPP)-4 Inhibitors

<table>
<thead>
<tr>
<th>Class/Main Action</th>
<th>Name(s)</th>
<th>Daily Dose Range</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP – 4 Inhibitors</strong></td>
<td>sitagliptin (Januvia)</td>
<td>25 - 100 mg daily – eliminated via kidney*</td>
<td>*If creat elevated, see med insert for dosing. *Side effects: headache and flu-like symptoms.</td>
</tr>
<tr>
<td><strong>“Incretin Enhancers”</strong></td>
<td>saxagliptin (Onglyza)+</td>
<td>2.5 - 5 mg daily – eliminated via kidney*, feces</td>
<td><strong>Can cause severe, disabling joint pain.</strong> Contact MD, stop med. Report signs of pancreatitis.</td>
</tr>
<tr>
<td></td>
<td>linagliptin (Tradjenta)</td>
<td>5 mg daily – eliminated via feces</td>
<td>+Saxagliptin and alogliptin can increase risk of heart failure. Notify MD for shortness of breath, edema, weakness, etc.</td>
</tr>
<tr>
<td></td>
<td>alogliptin (Nesina)+</td>
<td>6.25 - 25 mg daily – eliminated via kidney*</td>
<td>No wt gain or hypoglycemia. Lowers A1c 0.6%-0.8%.</td>
</tr>
</tbody>
</table>

http://diabetesed.net/pocket-cards-insulin-and-diabetes-meds
DPP-4 Inhibitors: Use in CKD

• Most DPP-4 inhibitors reduce dose
  ➢ Example:
    Sitagliptin (Januvia to 50mg : eGFR: 30-45)
    25mg when eGFR< 30
    vs.
    Linagliptin (Tradjenta) not renally cleared

• Safety data stage 1-4 CKD
• Limited data in ESRD

## CV Outcome Studies for DDP4-Is

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Primary endpoint</th>
<th>N</th>
<th>Follow-up time (years)</th>
<th>Mean age</th>
<th>Mean HbA1c levels (%)</th>
<th>CV status of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR TIMI</td>
<td>Saxagliptin versus placebo to standard of care</td>
<td>CV death, AMI, or stroke</td>
<td>18,206</td>
<td>2.1</td>
<td>≥40</td>
<td>≥6.5</td>
<td>CVD or high CV risk</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin versus placebo</td>
<td>CV death, AMI, unstable angina, or stroke</td>
<td>14,724</td>
<td>3</td>
<td>≥50</td>
<td>6.5–11</td>
<td>Pre-existing CVD</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin versus placebo to standard of care</td>
<td>CV death, AMI, or stroke</td>
<td>5380</td>
<td>1.5</td>
<td>≥18</td>
<td>6.5–11</td>
<td>Acute coronary syndrome within previous 15–90 days</td>
</tr>
</tbody>
</table>

DPP-4 Inhibitors and CV Protection?

• 4 large trials failed to show CV benefit
  ➢ **SAVOR-TIMI 53** (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial infarction) – **May increase CHF**
  
  ➢ **EXAMINE** (Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome) - **May increase CHF**
  
  ➢ **TECOS** (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) - neutral
  
  ➢ **CAROLINA Study** (Linagliptin) - neutral
DDP4-I and HIV

- Sitagliptin Reduces Inflammation and Chronic Immune Cell Activation in HIV+ Adults With Impaired Glucose Tolerance pilot 8 week trial

- Sixteen weeks of sitagliptin had no effect on sCD14 levels in virologically suppressed participants with HIV.

- CXCL10, a chemokine involved in atherogenesis that predicts non-AIDS events during ART, declined markedly with sitagliptin
DDP-4 Inhibitors and Potential Renal Benefit

Significant reductions in microalbuminuria and in proteinuria

DDP-4 Inhibitors and Liver Disease

- No improvement of fibrosis randomized, placebo-controlled trials of sitagliptin for NASH

- The hepatic protective effects of DPP-4 inhibitors may be from direct actions on hepatocytes via GLP-1 receptors and appear to occur irrespective of the degree of glycemic control

- HCV-infected T-cells may be responsible for the increased serum DPP-4 activity in patients with HCV infection

- Limited human clinical data likely safe to Child stage b

Summary: DPP-4 Inhibitors

- Mild glycemic benefit (0.6-0.8% HbA1c reduction)
- Can use in renal disease and some potential renal benefit
- Significant cost ($200 to $400/month)
- NO CV benefit -?? Harm for HF in those with or at risk for CHF
- Weight neutral
- Well tolerated/ few side effects so consider in those with compensated cirrhosis
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