

Diabetes Care for the HIV Clinician

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Outline

- Epidemiology and prevalence of diabetes mellitus and metabolic syndrome in HIV patients
- Clinical approach to the diabetes patient
- Therapies in the ambulatory setting
- Therapy in the hospital setting

Metabolic syndrome: a working definition

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin- *metabolic risk factors*- that appear to directly promote the development of atherosclerotic cardiovascular disease.

Criteria for Clinical Diagnosis of Metabolic Syndrome (MetS)- any 3 of the following:

Measure	Categorical Cutpoints
Elevated Waist Circumference	≥40 in (102 cm) in men ≥35 in (88 cm) in women
Elevated Triglycerides	≥150 mg/dl OR on drug treatment for triglycerides
Reduced HDL-Cholesterol	<40 mg/dl in men <50 mg/dl in women OR on drug treatment for HDL
Elevated Blood Pressure	≥130 SBP OR ≥85 DBP OR on drug treatment for BP
Elevated Fasting Glucose	≥100 mg/dl OR drug treatment for glucose

Metabolic syndrome and HIV

- The HIV Lipodystrophy Case Definition Study reported metabolic syndrome (MetS) prevalence rates 14-17% (among cohort with 57% prevalence of lipodystrophy)
 - Diabetes mellitus was present in 18% of those with MetS vs. 2% of those without
- MetS incidence rates are 12-14 per 100 patient-years in patients initiated on cART
 - Relative risk of developing DM increased 4-fold in those with metabolic syndrome at baseline and 4 to 5-fold in incident cases of MetS

Key Changes to 2010 ADA Standards: Diagnosis of Diabetes

- **Criteria for Diagnosis of Diabetes**

- **A1C $\geq 6.5\%$** using standardized test method*

OR

- Fasting plasma glucose (FPG) ≥ 126 mg/dl (8 hr fast)

OR

- 2 hour plasma glucose ≥ 200 mg/dl during a 75 gram oral glucose tolerance test (OGTT) OR

OR

- Hyperglycemic symptoms and random plasma glucose ≥ 200 mg/dl

- **Categories at increased risk for diabetes**

- **A1C 5.7-6.4%**

- FPG 100-125 mg/dl

- 2 hr glucose on OGTT 140-199 mg/dl

*National Glycohemoglobin Standardization Program (NGSP) Certified or DCCT Reference Assay

Hemoglobin A1c- a 90-day average glucose measure

HbA1c (%)	Est. Average Glucose (mg/dl)
5.5	111
6.0	126
6.5	140
7.0	154
7.5	169
8.0	183
8.5	197
9.0	212
9.5	226
10	240
11	269
12	298

Category	HbA1c range
Normal	<5.7%
At Risk for Diabetes	5.7-6.4%
Diabetes	≥6.5%

<http://professional.diabetes.org/GlucoseCalculator.aspx>

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Epidemiology of Diabetes in HIV

- HIV infection is associated with 2.2-fold increase in relative risk for diabetes
- Patients on Combination Antiretroviral Therapy (cART) have 4-fold increased relative risk of developing diabetes compared to seronegative controls, after adjusting for age and BMI
- Patients with lipodystrophy have higher prevalence of diabetes than those without
- Co-infection with HCV increases incidence of diabetes in HIV patients about 2-fold

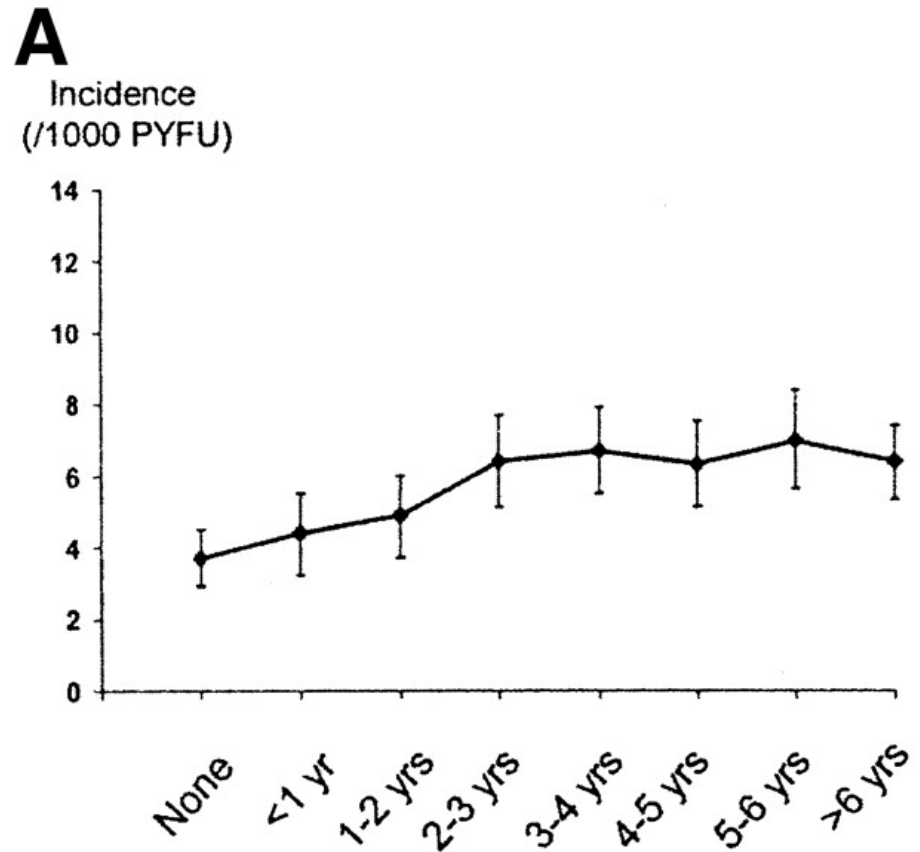
Risk Factors for Type 2 Diabetes

- Obesity
- Sedentary lifestyle
- Family History of diabetes
- Age
- History of gestational diabetes in women
- Ethnicity (African-American, Latino, Native American, Pacific Islander)
- Hypertension
- Dyslipidemia (low HDL/high triglycerides)
- History of CHD
- IFG/IGT

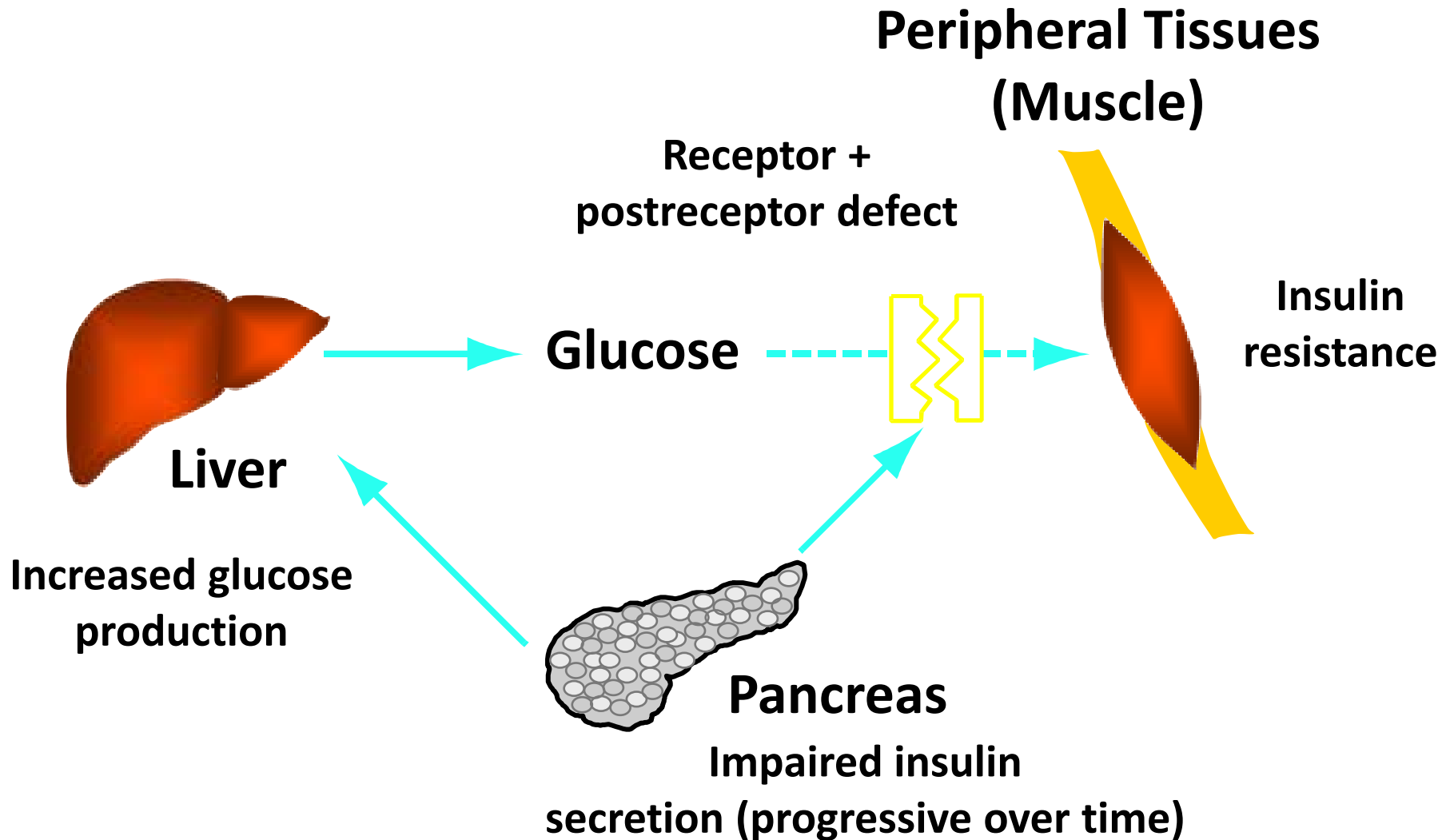
Incidence and Risk Factors for New-Onset Diabetes in HIV-Infected Patients

Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

- Prospective multi-center observational study of 33,389 HIV patients
- Baseline DM prevalence 2.85%
- DM incidence 7.72 per 1000 patient-years follow-up
- Incidence of new onset DM increased with cumulative exposure to cART (figure)
 - Strongest association with exposure to stavudine (adj. RR 1.19 per year exposure)
 - Other factors associated with increased risk of new onset DM: older age, male, greater BMI, non-white ethnicity



Causes of Hyperglycemia in Type 2 Diabetes



Pathophysiology of DM in cART

- Protease inhibitors (ritonavir, indinavir) can induce insulin resistance in vivo
 - PI can reduce adipocyte differentiation by altering adipogenic proteins (SREBP-1, PPAR- γ) and thus alter insulin sensitivity
 - PI can also reduce beta cell function and insulin secretion
 - Newer PI tend to have less adverse metabolic effects (atazanavir, saquinavir)
- NRTI (stavudine, AZT) can reduce insulin sensitivity by impairing mitochondrial function in adipocytes and inducing apoptosis

HIV Lipodystrophy



- Pathogenesis complex and related to HIV-therapy, patient-related factors, and HIV infection itself
- Prevalence 13-34% in HIV patients receiving HAART
- Can manifest as subcutaneous lipoatrophy and/or central lipohypertrophy



DM Screening and Prevention

- Given increased risk for DM in most HIV patients due to presence of conventional risk factors, cART, lipodystrophy, screening for DM is prudent
 - I would suggest annual assessment of fasting glucose and A1C
- Patients with IFG/IGT or metabolic syndrome on cART in particular should be encouraged to perform at least 150 minutes moderate exercise and follow appropriate diet (with weight loss goal if obese)
- Metformin can be considered in high-risk patients with IGT/IFG plus other risk factors (A1C>6%, HTN, family history, low HDL/high trig) who are obese and <60 years of age
 - Metformin can worsen lipoatrophy in some patients with lipodystrophy, however it may be useful in patients with predominant lipohypertrophy (Brown, T. T. J Clin Endocrinol Metab 2008;93:2937-2945)

Case 1

- 33 year old hispanic male with recently diagnosed HIV found to have random glucose of 227 on clinic visit
- BMI 34, A1C 8.1%, BP 128/76

Approach to the patient with newly diagnosed diabetes

- History
 - Hyperglycemic symptoms
 - Signs/symptoms of microvascular complications
 - Weight change
 - Associated co-morbidities (HTN, CVD, hyperlipidemia, chronic kidney disease, liver disease)
 - Current diet and exercise habits
- Exam
 - BP, weight, BMI
 - Cardiac exam, vascular exam
 - Foot exam
- Labs/Tests
 - A1C
 - Glucose
 - Comprehensive metabolic profile (lytes, creatinine, liver function profile)
 - Urine microalbumin or spot urine protein/creatinine ratio if established CKD
 - Fasting lipid profile
 - Resting ECG (if HTN, hyperlipidemia)

Diabetes Treatment Goals

- A1c goal in general is <7%
 - less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions and those with longstanding diabetes in whom the general goal is difficult to attain despite appropriate diabetes management
- BP goal <130/80
 - ACEI or ARB should be part of drug regimen
- Lipid goals
 - Generally LDL <100, though LDL <70 may be appropriate for patients with DM and CHD
 - Secondary targets of HDL >40-50 and trigs <150 are desirable but LDL reduction is primary goal
 - Statin is preferred agent for achieving LDL goals
- Patients should have screening for microvascular complications at appropriate intervals (foot exam, retina screening, urine microalbumin)
- Aspirin therapy for appropriate patients

Key Changes to 2010 ADA Standards: Antiplatelet therapy

- Consider aspirin therapy (75-162 mg/d) for 1st prevention in type 1 and type 2 DM patients at increased cardiovascular risk (10 year risk >10%); this includes most men >50 yrs or women >60 yrs with at least 1 additional risk factor (HTN, smoking, dyslipidemia, +family history, albuminuria)
- There is insufficient evidence to recommend aspirin in lower risk individuals (men <50 or women <60 yrs). Clinical judgment should be used in younger patients with multiple risk factors
- Aspirin should be used for 2nd prevention in patients with CVD (or clopidogrel 75 mg/d if aspirin allergic)

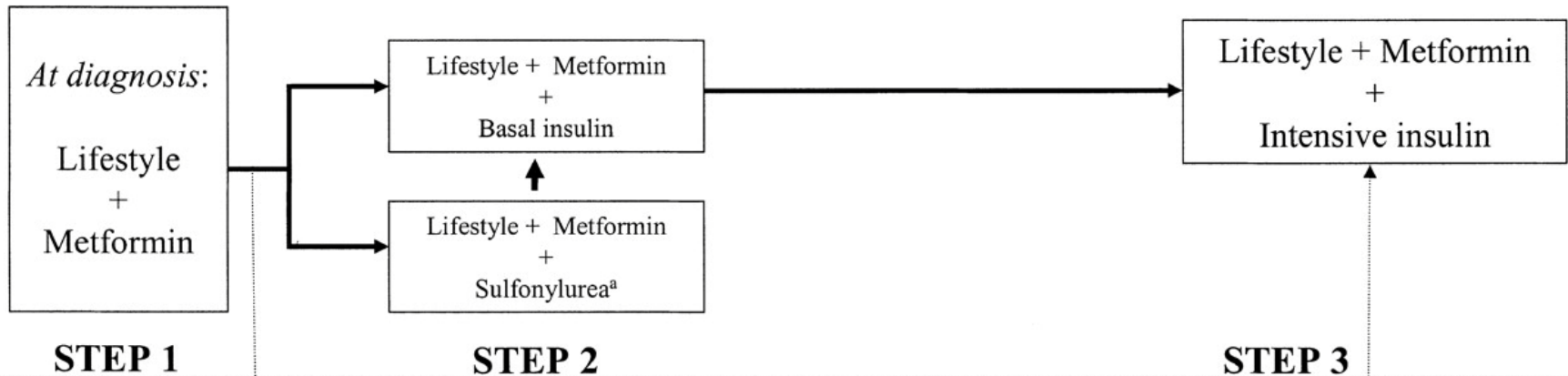
Why the change in guidelines for aspirin therapy for primary CV prevention in diabetes?

- No contemporary large single randomized controlled trial has shown clear benefit of ASA for primary prevention in patients with diabetes and no baseline CVD
- Meta-analysis of available trial data show trend towards benefit in prevention of CV events, but these are not conclusive
 - CHD events risk ratio (95%CI) 0.91 (0.79, 1.05)
 - Stroke risk ratio (95%CI) 0.85 (0.66,1.11)
- Need to integrate potential benefits and harms of aspirin therapy
 - Excess GI bleeding risk ~1-5 per 1000 per year
 - Excess Hemorrhagic stroke risk ~1 per 10,000 per year

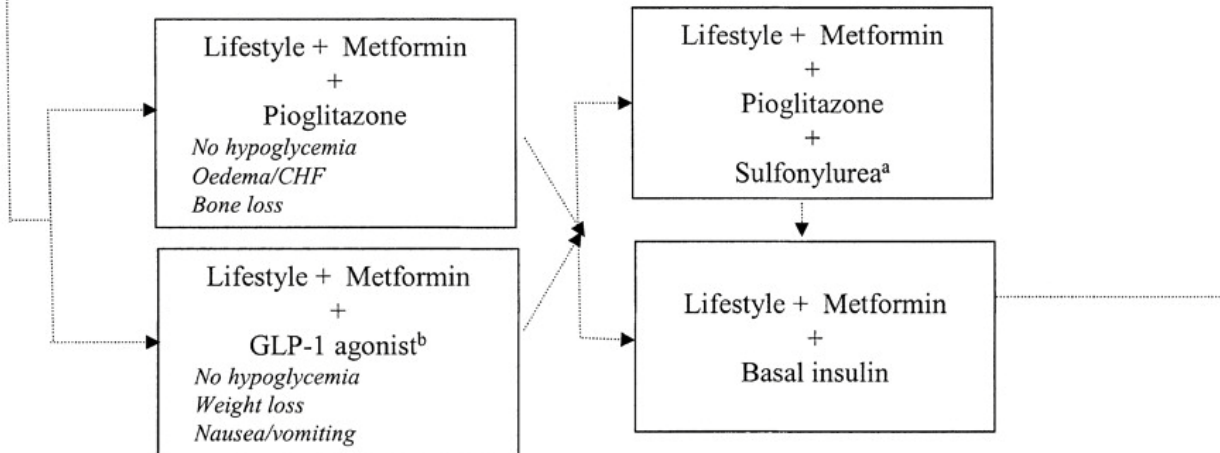


Getting to Goal: ADA/EASD Treatment Algorithm for Type 2 Diabetes

Tier 1: Well-validated core therapies



Tier 2: Less well-validated therapies



“Tier 1” Well-Validated Therapies

Tx	ΔA1C (%)	Advantages	Disadvantages
Lifestyle	1-2	-Broad benefits -No risk	-Poor adherence -Insufficient over time
Metformin	1-2	-Weight neutral -Cheap -Good tolerance	-GI side effects -Contraindicated renal failure
Sulfonylurea (glipizide, glimepiride, glyburide)	1-2	-Cheap -Rapidly effective -Good tolerance	-Hypoglycemia -Weight gain -Insufficient over time
Insulin	1.5-3.5 or >	-Rapidly effective -Broad utility -Durability	-Hypoglycemia -Weight gain -Monitoring/complexity

Caveats with “Tier 1” Therapies

- Initial glycemia influences treatment strategy (e.g. A1c 7.5% vs 9% vs 12% or more)
 - Lower initial A1C favors low hypoglycemic risk tx (lifestyle, metformin)
 - Very high A1C favors sulfonylurea and/or insulin as part of initial therapy
- Glyburide has significantly higher hypoglycemia risk, particularly in elderly patients, and should be avoided in favor of glimepiride or glipizide
- Insulin is your most effective and versatile tool
 - Rate of severe hypoglycemia with insulin in type 2 DM is low (1 to 3 events per 100 patient-years in trials)
 - The main advantage of newer insulin analogs is lower hypoglycemia risk. In patients without hypoglycemia issues, NPH and regular can work fine if lower cost is desired
- Metformin is generally ok in patients with heart failure as long as they are well compensated (NYHA class 1 or 2) and do not have concomitant renal dysfunction

“Tier 2” Therapies

Tx	Δ A1C (%)	Advantages	Disadvantages
TZD (rosiglitazone, pioglitazone)	0.5- 1.4	-Low hypoglycemia risk as monotherapy -Better durability	-Edema/CHF -Expensive -Weight gain
GLP1 agonist (exenatide, liraglutide)	0.5- 1.0	-Weight loss -Can use with SU, metformin, or TZD	-GI side effects -Expensive -Two Injections
Glinide (repaglinide, nateglinide)	0.5- 1.5	-Rapidly effective -Good tolerance	-Hypoglycemia, wt. gain -Expensive -3x/day dosing
DPP4 inhibitor (sitagliptin, saxagliptin)	0.5- 0.8	-Weight neutral -Can use with SU, metformin, or TZD	-Expensive -Limited data

Caveats with “Tier 2” Therapies

- Tier 2 agents are useful in patients with intolerance/contraindication to metformin who need combination therapy
- Can use combinations of agents that have low hypoglycemia risk (e.g. metformin + TZD, DPP4 inhibitor, or GLP1 agonist)
- Weighing individual cost-benefit and side-effect profile is important for selecting the right agent
- Generally, you are better off adding insulin than adding a third or fourth non-insulin agent in patients who are not meeting goal, particularly if A1c is $>8\%$

Caveats with DM therapies in HIV

- TZDs have shown some efficacy in improving metabolic parameters and fat distribution in HIV lipodystrophy, but results of clinical trials are mixed
- Need to select appropriate therapies in patients with HIV and advanced (stage 3 or >) chronic kidney disease
 - Metformin contraindicated
 - Use sulfonylureas with caution in advanced CKD as they can cause prolonged hypoglycemia

Which is better, pioglitazone or rosiglitazone?

- Many experts prefer pioglitazone based on available trial data (PROACTIVE) and effects on lipid profile (ADA/EASD Consensus Algorithm, Diabetes Care 2009; 32: 193-203)
- meta-analyses (NEJM 2007;356:2457-71 and JAMA 2007; 298:1189-95) have shown that rosiglitazone use is associated with increased risk for MI. However other clinical trials did not show excess MI risk in patients treated with rosiglitazone (BARI-2D, VADT, RECORD)
- A recent FDA regulatory action* announced 9/23/10 will be restricting access to rosiglitazone using Risk Evaluation and Mitigation Strategy (REMS)
- current users of rosiglitazone will only be able to continue using the medication if they acknowledge and document that they understand the risks associated with the drug
- only patients who cannot achieve control of diabetes on other medications and who decide not to take the alternative medication pioglitazone for medical reasons will be eligible to initiate rosiglitazone.
- Both agents increase the risk for edema, CHF, and fracture

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226976.htm#Q5> (*accessed 10/17/10)

Case 2

- 41 year old female with HIV, type 2 diabetes, hypertension, dyslipidemia
- Viral load undetectable on stable HAART
- Current DM regimen
 - Metformin 1000 mg bid
 - Glimepiride 4 mg daily
- Weight 190 pounds, BMI 33
- Fasting glucose has been in the 200 range
- Hba1c 9.2%

Insulin Therapy in Type 2 Diabetes: Indications



- Significant hyperglycemia at presentation
- Hyperglycemia despite maximal doses of oral agents
- Decompensation
 - acute injury, stress, infection
 - severe hyperglycemia with ketonemia and/or ketonuria
 - uncontrolled weight loss
- Surgery
- Pregnancy
- Renal disease
- Allergy or serious reaction to oral agents

Combination Therapy- Bedtime Basal Insulin + Daytime Oral Agents

- Goal is to normalize AM fasting glucose
- Bedtime NPH, Detemir, or Glargine can be used
- Oral medications continued during day
- Start at low dose (0.2-0.3 u/kg/day) and titrate up until AM fasting glucose <130 without nocturnal hypoglycemia

Insulin Titration Algorithm Example: Starting Basal Insulin

- Can begin basal insulin at **0.2-0.3 units/kg/day** at bedtime
- Can titrate up every 3-7 days based on average AM fasting glucose
- Most type 2 patients need **at least 0.4-0.8 units/kg/day** to get control

Avg. AM Glucose (mg/dl)	Dose change (units)
<80	-2
80-109	No change
110-139	+2
140-179	+4
≥180	+6

Case 3

- 64 year old male with HIV, type 2 diabetes, and hepatitis C, currently on 70/30 insulin
 - Dose: 60 units AM and 35 units PM
 - Glucose before breakfast ranges 140-170
 - Glucose midday is 110-180
 - Glucose before supper is 160-210
 - He intermittently has hypoglycemia in the early morning hours between 1-3 AM
- Hba1c 8.5%

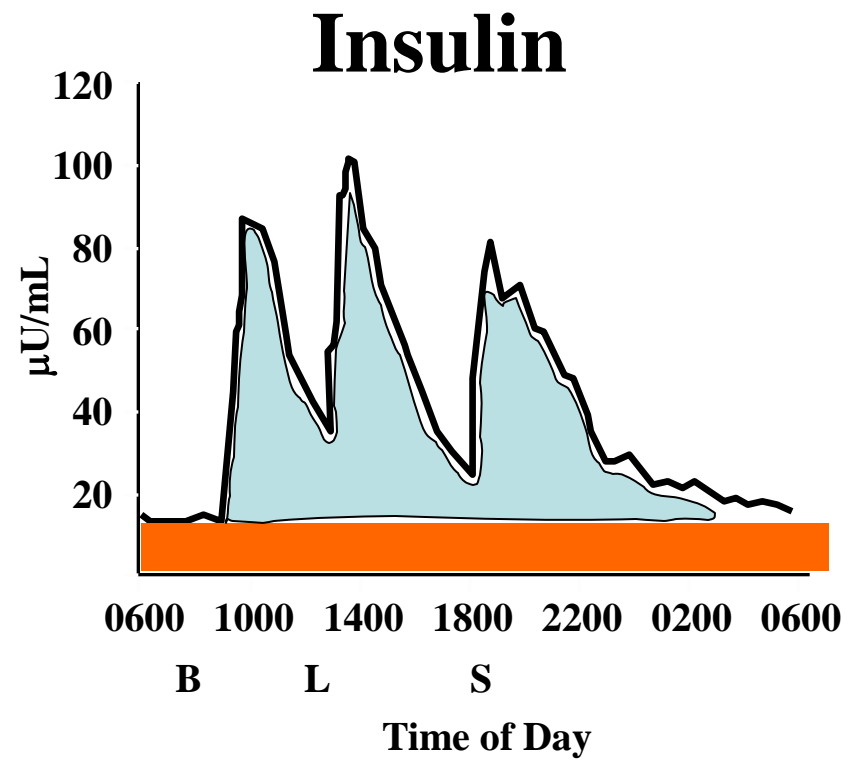
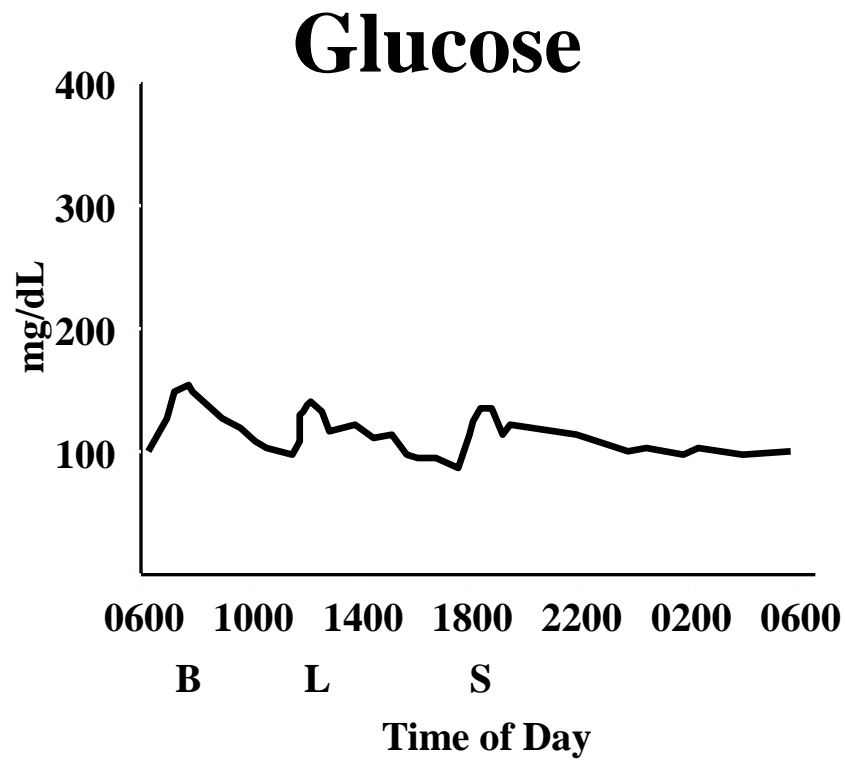
Approach to Patient on Insulin Therapy

- Type of diabetes
- Level of insulin resistance
- Regimen (How the patient actually takes insulin)
- Prior diabetes treatment
- Diet and exercise
- BG monitoring
- Hypoglycemia
- Glycemic control
- Compliance

Causes of Hypoglycemia

- Reduced intake
- malnutrition
- malabsorption
- adrenal insufficiency
- Renal/hepatic failure
- meal/insulin mismatch
- Drugs that potentiate oral hypoglycemics
- alcohol
- Exercise

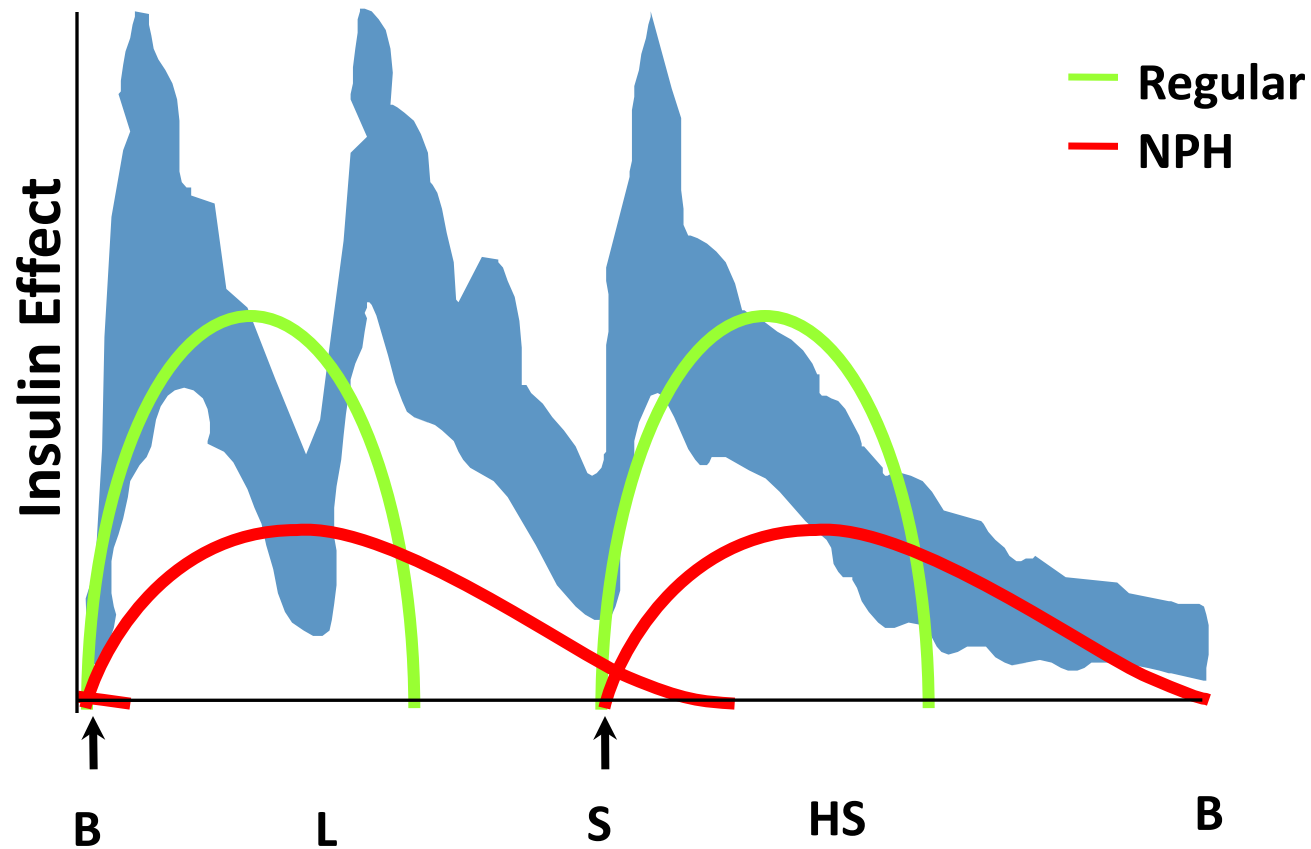
Normal Insulin and Glucose Patterns



Available Insulin Preparations

Insulin	Onset	Peak	Duration
Regular	30-60 min	2-4 h	4-6 h
Aspart, lispro, glulisine	5-15 min	1-2 h	4-5 h
NPH	1-3 h	5-8 h	13-18 h
Glargine	1-2 h	Flat	22-24 h
Detemir	1-2 h	Flat	22-24 h
75/25	15 min	1.5/2-4	4/6-12
70/30	1 h (R)	2/8 (R/N)	6/15 (R/N)

Twice-daily Split-mixed and 70/30 Regimens



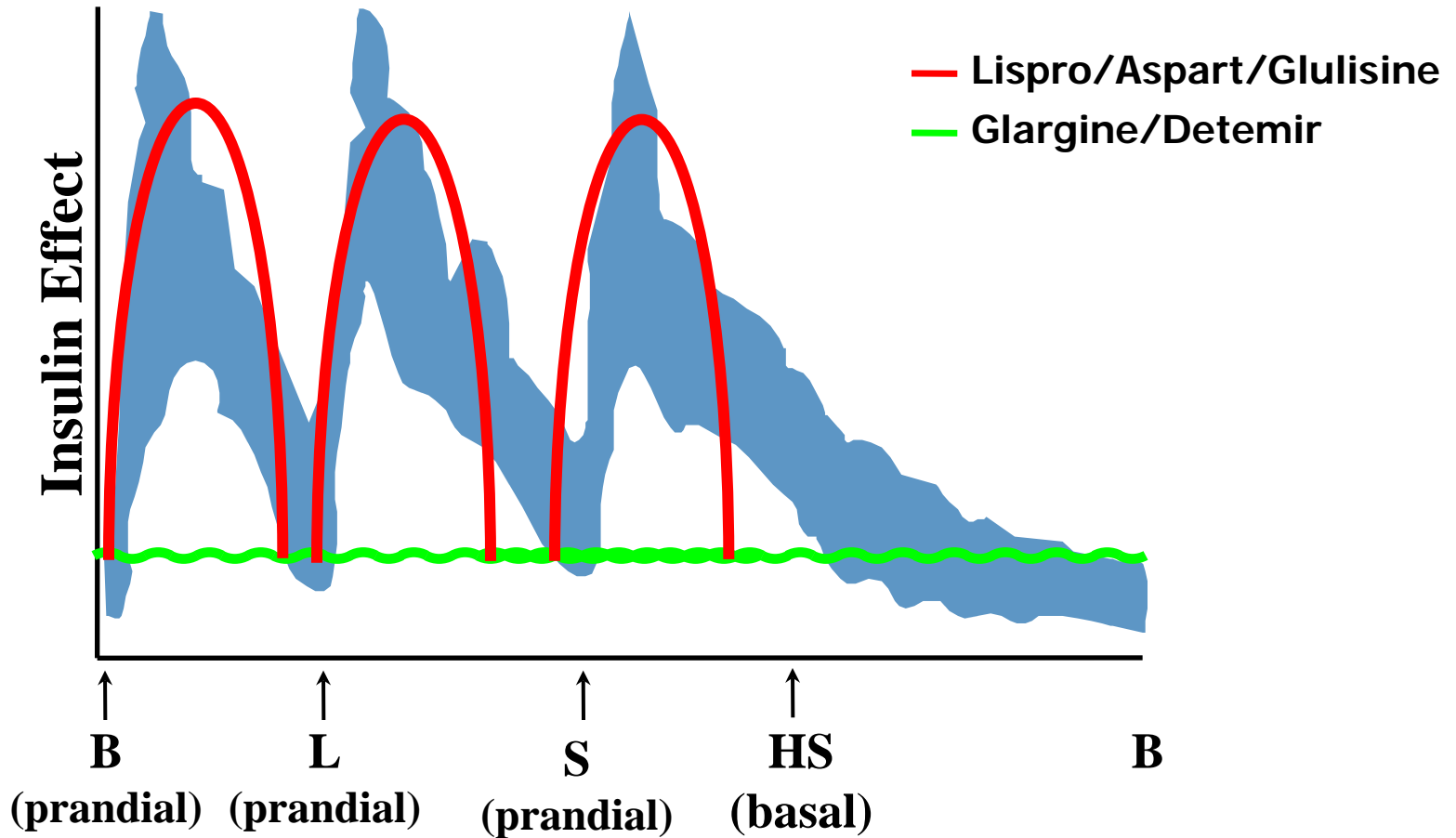


Thinking Like a Pancreas

The Basal/Bolus Insulin Concept

- **Basal Insulin**
 - Controls glucose levels between meals and overnight
 - Nearly constant levels
 - 50-60% of daily needs
- **Bolus Insulin (Mealtime or Prandial)**
 - Limits hyperglycemia after meals
 - Immediate rise and sharp peak at 1 hour
 - ~10% to 15% of total daily insulin requirement at each meal
- *For insulin replacement therapy, each component should come from a different insulin with a specific profile*

Multiple Daily Injections (“MDI”) Basal + Prandial



Choosing basal and meal insulin doses for intensive insulin therapy

- TDD divided as 40-50% basal, 50-60% meal
- Average Basal Requirement for type 1 DM 0.2-0.4 u/kg/day
- Average Basal Requirement for type 2 DM 0.4-0.8 u/kg/day
- Meal Dose can be fixed or varied by carbohydrate intake
 - Meal dose for type 1: 0.05-0.08 u/kg/meal
 - Meal dose for type 2: 0.1-0.2 u/k/meal
 - CHO ratio (units insulin:Grams CHO) for type 1 = 1 :15 to 1:20
 - CHO ratio for type 2= 1:10 to 1:3

Top Pitfalls of Insulin Therapy

- “Threatening” patients with insulin therapy when they have uncontrolled diabetes on oral agents
- Failure to intensify therapy
- Poor Dosing
- Inadequate patient education
- Failure to address hypoglycemia

Roger

- Patient admitted to VUMC 7-10, after falling (syncope?), blood glucose 673, AG 10;
 - Meds on admission:
 - LPVr + NVP + raltegravir; pioglitazone 15 mg daily; pravastatin 40 mg daily; amitriptyline 150mg at bedtime; procrit 40,000 Units weekly; acyclovir 400 mg daily; lisinopril 20 mg daily;
 - Patient is disoriented on admission, negative work-up, clears somewhat and wants to return home to independent living.

Roger

- Sixty two year old AA male:
 - Diagnosed HIV + in 1989;
 - On sixth regimen: NVP and LPVr since 2002; raltegravir substituted for TFV in 1/09; eight other medications.
 - Co-morbidities: Type II DM, HTN, CMV retinitis, MAC, dyslipidemia, peripheral neuropathy, lipodystrophy, HBV sAg+ , chronic kidney disease; PVD, depressive disorder; CAD (NSTEMI, stented);
 - Labs: CD4 670/25%; HIV-1 RNA <48; Hgb A1C: 13.2; Creatinine 2.74; HBV 2400 copies/ml;

Managing diabetes in non-critically ill hospital patients

2010 ADA Recommendations

- All patients with diabetes should be identified with diabetes in the medical record
- All patients with diabetes should have an order for blood glucose monitoring
- All patients with diabetes should have an A1C obtained unless results already available within the previous 2-3 months
- Critically ill patients target range 140-180 mg/dl recommended, with therapy initiated for glucose >180 mg/dl
- Non-critically ill patients:
 - Fasting/premeal glucose target <140 mg/dl
 - Postprandial/random glucose <180 mg/dl
- A plan for treating hypoglycemia should be established for each patient.
- A diabetes education plan including “survival skills education” and follow up should be developed for each patient
- Patients with hyperglycemia without a diagnosis of diabetes should have appropriate follow up testing and care arranged at discharge
 - **A1c 6.5 or > meets criteria for diagnosis of diabetes**

Managing Oral Diabetes Agents

- If a patient is clinically stable, eating, has been under acceptable glycemic control, and no contraindications exist, oral agent(s) may be continued/resumed in medical and surgical patients who are approaching discharge.
- All other patients should be placed on insulin if persistently hyperglycemic

An Approach to Insulin Therapy

THE 4 STEPS

1. Basal Insulin (Long Acting)
2. Prandial/Bolus Insulin (Meal)
3. Correction Insulin (Sliding Scale)
4. Monitoring and hypoglycemia management

Regimen	Insulin total daily dose (TDD)	Basal dose Unit/kg/day	Bolus (meal) dose unit/kg/meal	Scale formula BG-100/X X=	Correction unit dose range BG 140-300
Low	<30	0.2	0.05	50	1-4
Moderate*	30-59	0.3	0.05	30	1-7
High	60-89	0.4	0.1	20	2-10
Very high	90 or >	0.5	0.15	15	3-13

*Most patients on oral agent therapy alone for diabetes can be treated with this regimen as an initial insulin dosing strategy

Roger

- 62 yr old AA male with HIV, Type 2 DM, HTN, CMV retinitis, MAC, dyslipidemia, peripheral neuropathy, lipodystrophy, HBV sAg+ , chronic kidney disease; PVD, depressive disorder; CAD
- Patient admitted to hospital after falling (syncope?), blood glucose 673, AG 10; weight 100 kg
 - Meds on admission:
 - LPVr + NVP + raltegravir; pioglitazone 15 mg daily; pravastatin 40 mg daily; amitriptyline 150mg at bedtime; procrit 40,000 Units weekly; acyclovir 400 mg daily; lisinopril 20 mg daily;
 - Labs: CD4 670/25%; HIV-1 RNA <48; Hgb A1C: 13.2; Creatinine 2.74; HBV 2400 copies/ml;

Roger's orders

- Discontinue pioglitazone
- Monitor Glucose Q4 hours at 4:00-8:00-12:00-16:00-20:00-00:00
- If glucose <70 give 15 grams glucose gel PO or ½ Amp D50 IV
- Glargine* insulin 40 units subcut. QHS (0.4 units/kg/day)
 - Give even if NPO
- Aspart** insulin 10 units TID-AC (0.1 units/kg/meal)
 - Hold if NPO
- Aspart** correction scale Q4 hours at 4:00-8:00-12:00-16:00-20:00-00:00 (2 units per 40 mg/dl glucose over 140)
 - Glucose <140: none
 - Glucose 140-180: +2 units
 - Glucose 181-220: +4 units
 - Glucose 221-260: +6 units
 - Glucose >260: +8 units
- Once blood glucose <200 consistently, change monitoring and correction scale frequency to QAC HS

*Alternative basal insulin: NPH 20 units bid, or insulin detemir 40 units QHS

** Alternative meal/correction insulin: lispro, glulisine. If regular insulin used would consider adjusting correction scale to q6H if renal insufficiency present

Adjusting for tests and procedures

- Patients should get IV dextrose if NPO for a prolonged period (>6-8 h)
 - A lower fluid volume of D10 can be used in patients with a fluid restriction
- Well controlled patients on stable basal / bolus regimen generally can get full basal dose of insulin
 - If uncertain about glycemia on current basal dose and not currently hyperglycemic, can reduce basal dose just prior to procedure by 25-30% as a precaution
- hold all oral diabetic agents
- Type 1 diabetes patients **MUST GET BASAL INSULIN, usually full dose**

Hospital Diabetes Management- Key Points

- Avoid oral diabetes agents in sick patients
- Reassess and adjust your diabetes therapy **daily**
- Provide clear orders for monitoring and hypoglycemia management / prevention
- Use insulin to control hyperglycemia: 3 components
 - Basal (**ALWAYS** in patients with type 1 or insulin requiring type 2 DM)
 - Bolus (meal)
 - Correction
- Avoid a “one size fits all” approach to insulin therapy
- Take opportunity to intensify therapy at discharge in patients with poorly controlled DM
- Arrange follow up for patients with newly discovered hyperglycemia and diabetes or uncontrolled diabetes

Roger- Discharge Planning

- Patient is given basic diabetes education and practices insulin self-administration in hospital
- After discussion with the patient and assessment of his current lifestyle, resources, and comorbid conditions, the patient is discharged on basal/bolus insulin with glargine and lispro insulin
- Patient is scheduled for close follow up in 1 week after discharge for his DM and HIV
- He is given clear instructions about monitoring and what to do for hyper- and hypoglycemia

Summary

- Diabetes is a common comorbid condition in HIV patients
- Selection of appropriate therapy and titration are crucial to success
- Insulin is your friend