



DIABETES & HIV/AIDS DYABET E SIDA

Presented By: Suzie Richardson-Armas, FMG, MPH, PA-C, AAHIVS

New Health Community Centers & New World Health Foundation



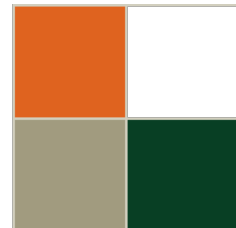
UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE



OBJECTIVES

After this training, participants will be able to:

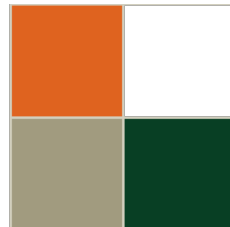
- Define diabetes mellitus type II and human immunodeficiency virus disease and their relationship
- Describe how diabetes and HIV is diagnose
- Discuss which HIV medicines may increase blood glucose levels and lead to type 2 diabetes.
- How diabetes type 2 and HIV can be controlled.



OBJEKTIF

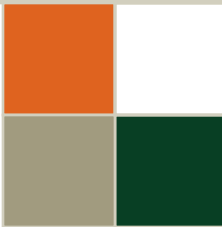
Aprè Fòmasyon sa-a, patisipan yo ap kapab:

- Defini Dyabet Mellitus Tip 2, Maladi VIH ak relasyon ant 2 malady sa yo.
- Diskite ki medikaman pou VIH ki ka ogmante sik nan san e bay maladi Dyabet tip 2.
- Ki jan ou ka kontwole Dyabet tip 2 ak VIH.



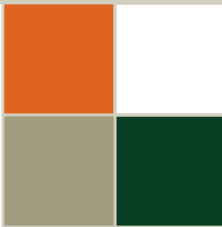
DEFINITIONS

- Acquired immunodeficiency syndrome (**AIDS**) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (**HIV**).
- By damaging your immune system, **HIV** interferes with your body's ability to fight the organisms that cause disease. **HIV** is a sexually transmitted infection.



DEFINITIONS

- Diabetes is a disease in which levels of blood glucose (also called blood sugar) are too high. Glucose comes from the breakdown of the foods we eat and is our main source of energy.



RISK OF DIABETES FOR HIV-INFECTED PATIENTS

Consists primarily of:

- Traditional factors
- Some PIs and NRTIs



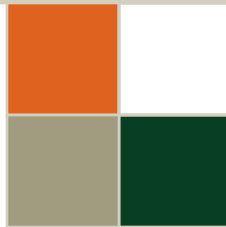
RISK FACTORS INCLUDE

- Family history of diabetes
- Increasing age
- Obesity
- Lipoatrophy
- Hepatitis C
- Medications

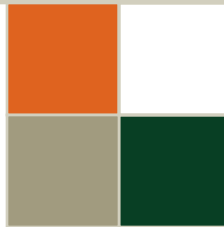
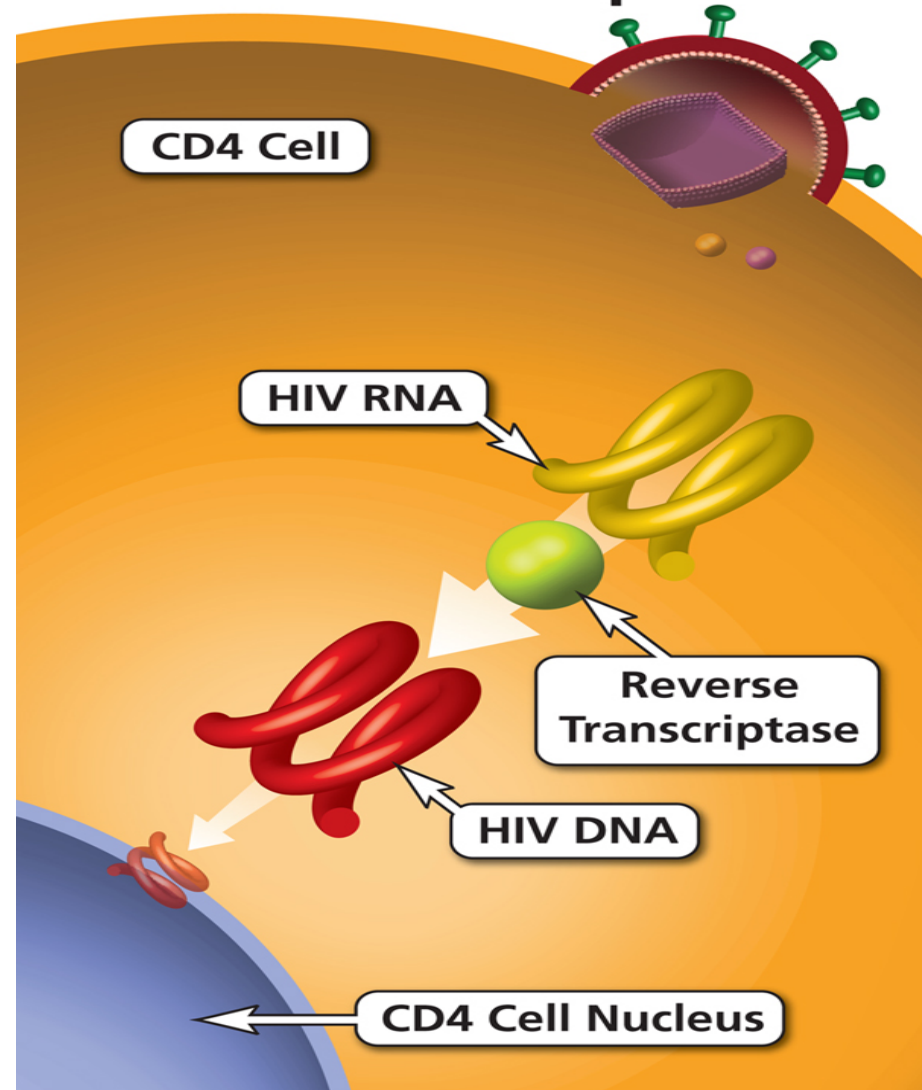
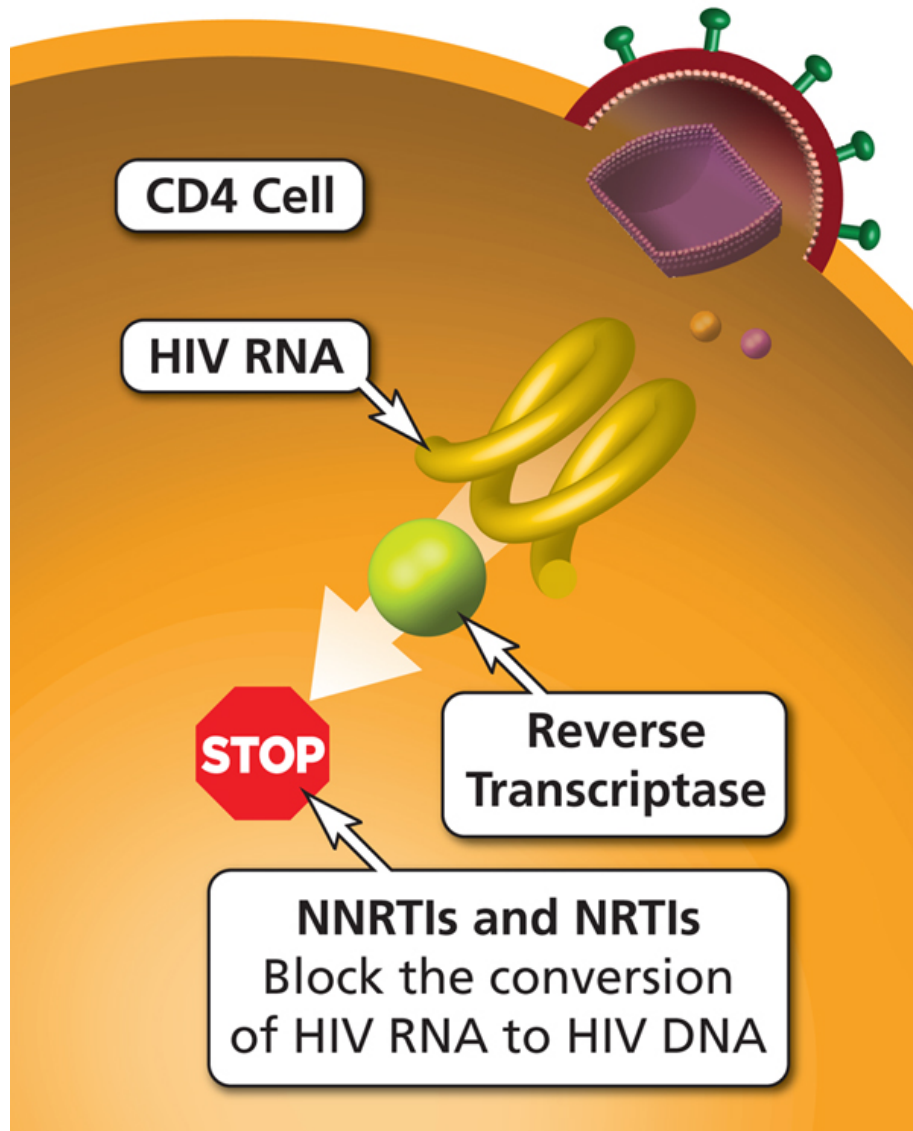


NRTI'S

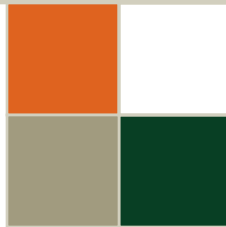
- When HIV infects a CD4 cell in a person's body, it copies its own genetic code into the cell's DNA. In this way, the cell is then "programmed" to create new copies of HIV. HIV's genetic material is in the form of RNA. In order for it to infect CD4 cells, it must first convert its RNA into DNA. HIV's reverse transcriptase enzyme is needed to perform this process.
- NRTIs, sometimes called "nucleoside analogues" or "nukes," contain faulty versions of the building blocks (nucleotides) used by reverse transcriptase to convert RNA to DNA. When reverse transcriptase uses these faulty building blocks, the new DNA cannot be built correctly. In turn, HIV's genetic material cannot be incorporated into the healthy genetic material of the cell and prevents the cell from producing new virus



Reverse Transcription



<u>Combivir*</u>	zidovudine + lamivudine	ViiV Healthcare
<u>Descovy</u>	emtricitabine + tenofovir alafenamide	Gilead Sciences
<u>Emtriva</u>	emtricitabine	Gilead Sciences
<u>EpiVir*</u>	lamivudine	ViiV Healthcare
<u>Epzicom*</u>	abacavir + lamivudine	ViiV Healthcare
<u>Retrovir*</u>	zidovudine	ViiV Healthcare
<u>Trizivir</u>	abacavir + zidovudine + lamivudine	ViiV Healthcare
<u>Truvada</u>	tenofovir disoproxil fumarate + emtricitabine	Gilead Sciences
<u>Videx EC*</u>	didanosine	Bristol-Myers Squibb
<u>Viread</u>	tenofovir disoproxil fumarate	Gilead Sciences
<u>Zerit*</u>	stavudine	Bristol-Myers Squibb
<u>Ziagen*</u>	abacavir	ViiV Healthcare



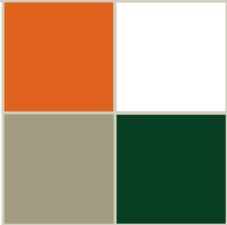
MEDICATIONS THAT INCREASE DIABETES RISK

- PIs: Most (except unboosted ATV have been implicated, particularly:
 - IDV
 - Full-dose RTV
 - LPV/r



PROTEASE INHIBITORS (PIs)

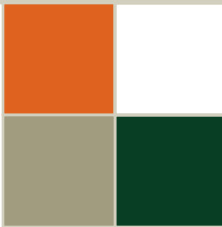
- The third group of drugs is the protease inhibitors (PIs)
- Once HIV has infected a cell and made copies of itself, it uses an enzyme called protease to process itself correctly so it can be released from the cell to infect other cells. These medicines work by blocking protease.



PROTEASE INHIBITORS (PIs)

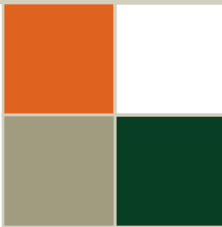
Nine PIs are available:

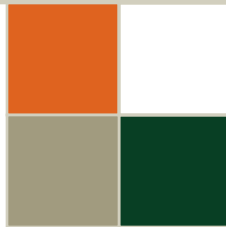
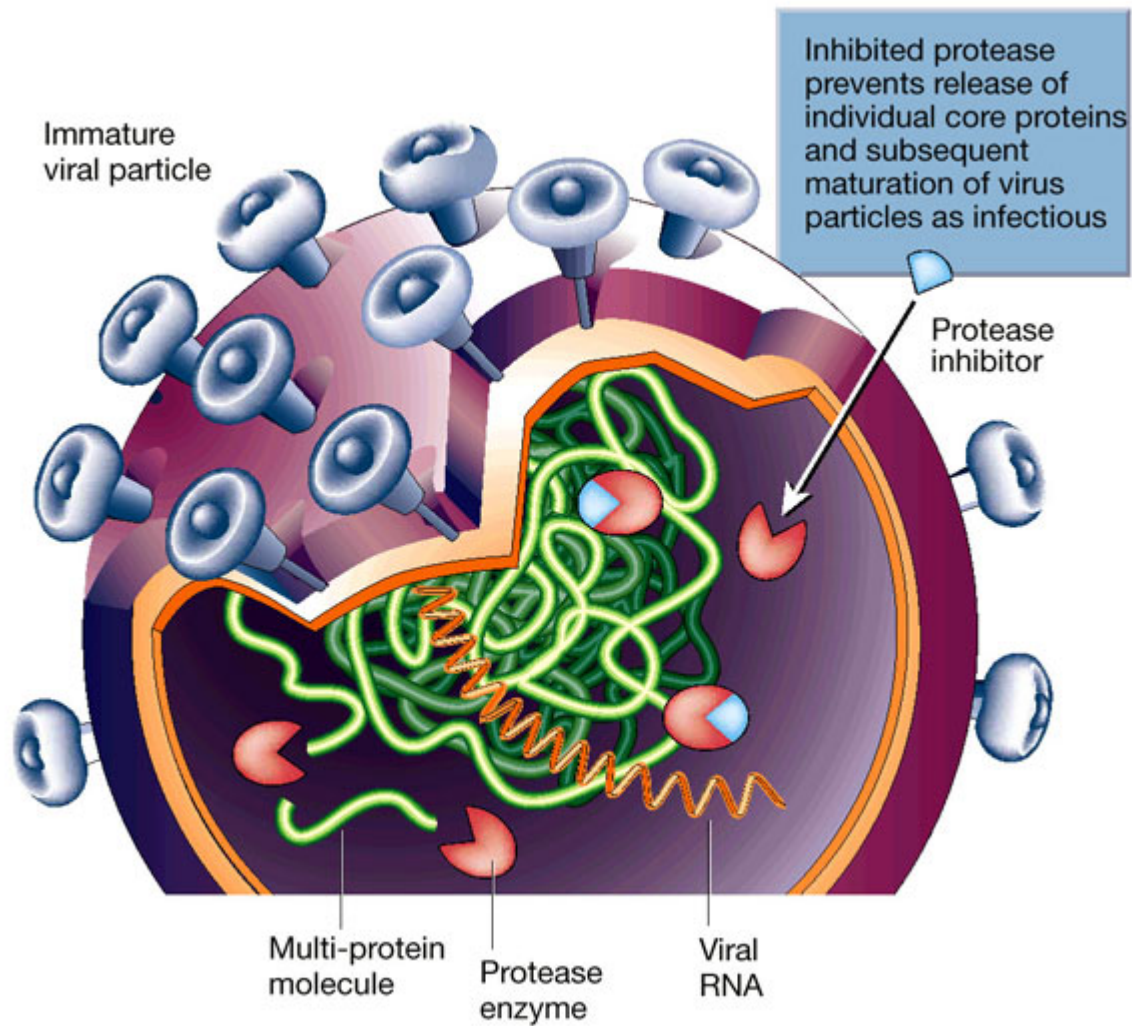
- Aptivus[®] (tipranavir)
- Crixivan[®] (indinavir)
- Invirase[®] (saquinavir)
- Kaletra[®] (lopinavir + ritonavir combined in one tablet)
- Lexiva[®] (fosamprenavir)
- Norvir[®] (ritonavir)
- Prezista[®] (darunavir)
- Reyataz[®] (atazanavir)
- Viracept[®] (nelfinavir)



PROTEASE INHIBITORS (PIs)

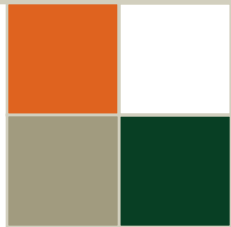
- Many PIs are recommended or approved for use only with another drug that "boosts" their effect. One of these is low-dose Norvir[®], the other is a non-HIV drug called Tybost[®] (cobicistat).
- Several combination tablets that include a "booster" plus a PI are:
 - Evotaz[®] (Reyataz[®] + Tybost[®])
 - Prezcobix[®] (Prezista[®] + Tybost[®])
 - Kaletra[®] (lopinavir + Norvir[®])





OTHER MEDICATIONS THAT INCREASE DIABETES RISK INCLUDE

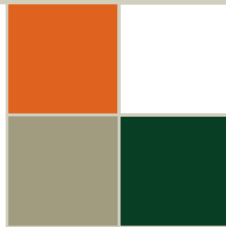
- Niacin
- Human growth hormone
- Corticosteroids
- Antipsychotics - Including:
 - Olanzapine
 - Quetiapine
 - Ziprasidone
- Pentamidine



BACKGROUND

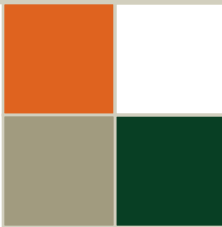
New-onset diabetes is estimated to occur in:

- 1-6% of HIV-infected patients on PIs.
- In one early study, 7% of patients on PIs were diagnosed with diabetes using the oral glucose tolerance test (OGTT).
- The same study showed that an additional 16% of patients had impaired glucose tolerance (IGT).



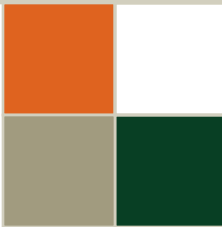
BACKGROUND

- The incidence of new-onset hyperglycemia among HIV-infected patients on ARV therapy (ART) has been reported as about 5%, on average.
- Even if fasting glucose levels remain normal in patients taking ARVs, up to 40% of those on a PI-containing regimen will show impaired glucose tolerance.
- The etiology of insulin resistance and hyperglycemia in HIV-infected patients probably is multifactorial, with varying contributions from traditional risk factors (e.g., obesity, family history), comorbid conditions (e.g., hepatitis C virus infection), and ARV-related factors (e.g., direct effects of exposure to NRTIs, hepatic steatosis, and fat redistribution). PIs, cumulative



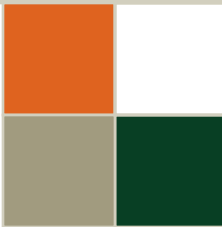
BACKGROUND

- The pathogenesis of insulin resistance among patients on PIs is not fully understood. It is hypothesized that inhibition of the GLUT-4 insulin-stimulated glucose-transport system by some PIs plays a role.
- When NRTIs have affected fat distribution, lipolysis increases, which can lead to a higher risk of insulin resistance.
- Increased insulin resistance is seen among patients who have developed lip hypertrophy, with a dorsocervical fat pad ("buffalo hump") or increased upper chest fat or intraabdominal fat.
- Lipoatrophy is associated with higher 2- hour glucose levels on OGTT.



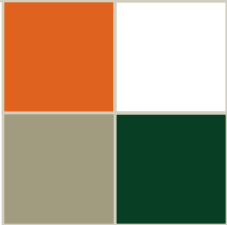
MONITORING

- Patients who have preexisting diabetes should be monitored closely when starting ART; some experts would consider avoiding PIs for these patients, if other options are feasible.
- Alternatively, PIs with favorable metabolic profiles (e.g., atazanavir) may be preferred for such patients.
- Patients with no history of diabetes should be advised about the warning signs of hyperglycemia (polydipsia, polyuria, and polyphagia) and the need to use diet and exercise to maintain an ideal body weight.



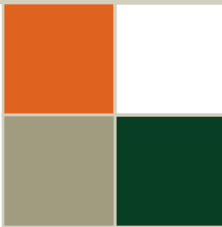
GLUCOSE METABOLISM

- Those who are about to begin ART
- Those on an ARV regimen that includes a PI
- Those with extensive exposure to NRTIs
- Those who are obese or overweight
- Those with central fat accumulation or lipodystrophy



DISORDERS OF GLUCOSE METABOLISM

- **Insulin resistance**
- **Impaired glucose tolerance:** glucose 140-199 mg/dL 2 hours after a 75 g oral glucose load
- **Impaired fasting glucose:** glucose 100-125 mg/dL after an 8-hour fast
- **Diabetes mellitus**



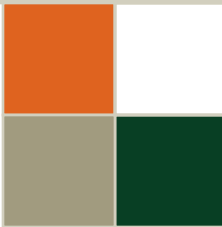
INSULIN RESISTANCE

- **Insulin resistance:** a state in which higher concentrations of insulin are required to exert normal effects; blood glucose levels may be normal but fasting insulin levels may be high because of compensatory insulin secretion by the pancreas.
- Failure of target tissues to respond appropriately to insulin
- This leads to decreased muscle uptake of glucose and sometimes to increased hepatic gluconeogenesis. Insulin production is increased to overcome the insulin resistance and maintain glucose homeostasis. Over time, even high levels of endogenous insulin may not control serum glucose levels, resulting in IGT, followed by diabetes.



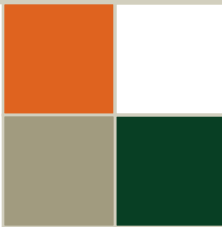
DIABETES MELLITUS

- **Diabetes mellitus:** any of the following four criteria may be used (results must be confirmed by retesting on a subsequent occasion):
 - Fasting glucose ≥ 126 mg/dL
 - Glycosylated hemoglobin (HbA1c) level $\geq 6.5\%$
 - 2-hour glucose level ≥ 200 mg/dL during glucose tolerance testing
 - Random glucose values ≥ 200 mg/dL in the presence of symptoms of hyperglycemia



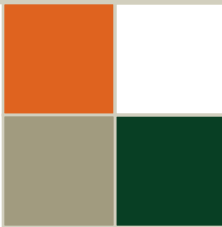
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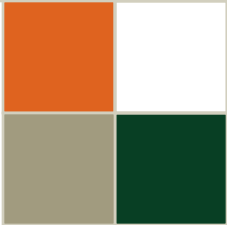
PATIENT'S HISTORY

- **Risk factors:**
 - Family history of diabetes
 - Obesity
 - Habitual physical inactivity
 - Racial or ethnic heritages (higher risk: African-American, Hispanic, Native American, Asian/Pacific Islander)
 - Gestational diabetes or delivery of an infant weighing >9 lb (4.1 kg)
 - Current pregnancy
 - Hepatitis C virus coinfection
 - Polycystic ovary syndrome
 - Medications, including PIs, NRTIs, niacin, corticosteroids, antipsychotics



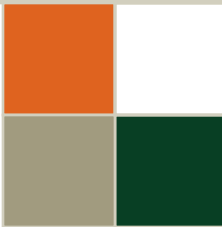
COMORBIDITIES

- Hypertension
- Low level of high-density lipoprotein (HDL)
- Elevated triglycerides
- Coronary artery disease
- Fat redistribution on ARVs
- Smoking



PHYSICAL EXAM

- Blood pressure, weight, body mass index (BMI)
- Heart and lung examination
- Peripheral pulses
- Examination of neck, dorsocervical area, breasts, and abdomen for fat accumulation; measurement of waist circumference
- For patients with hyperglycemia or diabetes:
 - Retinal examination (refer to ophthalmologist for dilated examination)
 - Visual inspection of feet (for ulcers)
 - Sensory examination of feet (for neuropathy)



DIAGNOSTIC EVALUATION

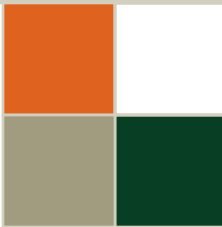
- Determine whether the patient has normal blood glucose, impaired fasting glucose, or diabetes.
- Most experts recommend routine checks of fasting blood glucose levels at baseline and within 3-6 months after starting or changing ART, if baseline results are normal. For patients with normal glucose levels, recheck every 6-12 months. Monitoring should be more frequent if abnormalities are detected or if any additional risk factors exist. Patients with risk factors for diabetes must be counseled about prevention of hyperglycemia before starting ART.
- The role of 2-hour postprandial glucose measurements or the 75 g oral glucose tolerance test for diabetes is uncertain but these screenings may be appropriate for patients with multiple risk factors. The use of HbA1c testing to screen for diabetes has yet to be validated for the HIV-infected population. Of note, HbA1c values may underestimate glycaemia in HIV-infected patients, especially in the setting of elevated red blood cell mean corpuscular volume (MCV) (e.g., owing to zidovudine) or anemia.



DIAGNOSTIC EVALUATION

For patients with diabetes, monitor the following:

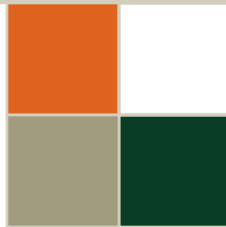
- HbA1c, every 3 months for patients who have elevated HbA1c or whose therapy has changed, every 3-6 months for patients with stable and adequate glucose control
- Fasting lipid panel
- Electrolytes, creatinine, estimated glomerular filtration rate (eGFR)
- Urine albumin/creatinine ratio (microalbuminuria: 30-299 mg/g)



TREATMENT

Patients with insulin resistance:

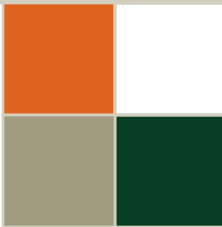
- For patients with insulin resistance who have normal blood glucose levels, current evidence is inadequate to recommend drug treatment. However, it may be possible to prevent the development of diabetes, and lifestyle modifications can be recommended, including exercise, avoidance of obesity, weight loss if indicated, and diet changes. Weight loss is strongly recommended if the patient is overweight. Refer the patient to a dietitian, if possible. Studies of insulin resistance in HIV-infected individuals are under way, and patients with access to clinical trials may be referred to these studies.
- Patients with insulin resistance and hyperglycemia require treatment. A trial of lifestyle modifications may be attempted, including weight loss (if indicated), diet changes, and exercise.
- For patients with diabetes and those whose lifestyle changes are not adequate to control blood glucose, specific treatment should be started.



TREATMENT

Patients with diabetes:

- Treatment should be instituted to control blood sugar and to modify other cardiovascular risk factors, with the aim of preventing heart disease and other end-organ disease.
 - Control glucose: maintain the HbA1c level at <7%, while avoiding hypoglycemia.
 - For hyperglycemia that is associated with the use of PIs, switching to an alternative agent (e.g., a nonnucleoside reverse transcriptase inhibitor, an integrase inhibitor, or a different PI) may be effective if the HIV treatment history and resistance profile permit.
 - Metformin usually is the initial drug of choice for overweight patients; other options include sulfonylureas and thiazolidinedione.
 - Metformin can worsen lipoatrophy and should be avoided in the presence of significant lipoatrophy. Metformin increases risk of lactic acidosis; it should not be used for patients with elevated serum creatinine (>1.5 mg/dL in men or >1.4 mg/dL in women), hepatic impairment, or metabolic acidosis.
 - Sulfonylureas may cause hypoglycemia. In starting therapy, shorter-acting agents (e.g., glipizide) may be preferable to longer-acting agents (e.g., glyburide). Some agents should not be used for patients with renal impairment (CrCl <50 mL/min).
 - Thiazolidinedione's should be avoided in patients with significant liver disease. Rosiglitazone may increase the risk of myocardial infarction and death (study results conflict); both rosiglitazone and pioglitazone have been associated with congestive heart failure and are contraindicated for use by patients with this condition.



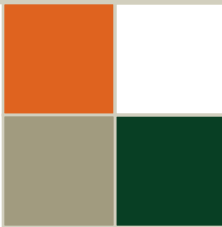
TREATMENT

- Treat dyslipidemia: maintain low-density lipoprotein (LDL) at <100 mg/dL and maintain triglycerides at <150 mg/dL. (Note that diabetes is considered a coronary heart disease equivalent state when evaluating goals for lipid management; see chapter [Dyslipidemia](#).)
- Treat hypertension: Maintain systolic blood pressure at <130 mm Hg and diastolic blood pressure at <80 mm Hg.
- Reduce cardiovascular risks through lifestyle modifications such as smoking cessation, exercise, weight loss, nutritional counseling, and moderation of alcohol intake.
- Decrease the risk of end-organ complications:



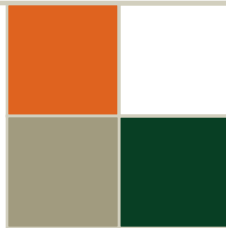
TREATMENT

- Measure urine microalbumin and creatinine; if the urine albumin/creatinine ratio is >30 mg/g, treat with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) to slow the progression of nephropathy.
- Schedule annual retinal examination by an ophthalmologist.
- Perform an annual foot examination.
- Start aspirin therapy (75-162 mg daily) if the patient has evidence of macrovascular disease or a history of vascular events. Consider daily aspirin for those with increased coronary heart disease risk (e.g., men >50 years and women >60 years of age with ≥ 1 coronary heart disease risk factor, such as a family history of coronary artery disease or a history of smoking).



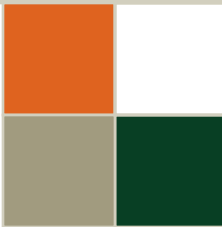
SWITCHING ART REGIMENS

- For patients who are taking ARV agents that may be causing or exacerbating hyperglycemia, consider discontinuing the problematic ARVs if safe and effective alternatives are available.
 - For example, substitute ATV, an NNRTI, or integrase inhibitor in place of a PI, or an unboosted PI (eg, ATV or FPV) for an RTV-boosted PI.
 - Avoid d4T.
- Before making ARV substitutions, carefully consider the possible effect on HIV virologic control and the potential adverse effects of new ARVs.
- In some cases, antidiabetic agents may still be necessary after ARV substitution.
- Reinforce lifestyle interventions at every visit.
- Check HbA1c every 3 months until the goal is reached and then at least every 6 months. The interventions should be changed if HbA1c is above goal.
- Thiazolidinedione's are nonformulary within the VHA.



INSULIN REGIMEN SELECTION

- Optimal insulin dosing mimics physiologic insulin release and consists of a basal component along with a prandial component, which is used to metabolize ingested carbohydrates.
- Individualization of insulin therapy is critical for ensuring optimal glycemic control.
- SMBG is critical to successful glycemic control with insulin.
- Patients should be educated regarding symptoms of hypoglycemia (eg, sweating, anxiety, disorientation, tachycardia) and instructed to ingest hard candy, juice, or another rapidly absorbed glucose source if symptoms occur.



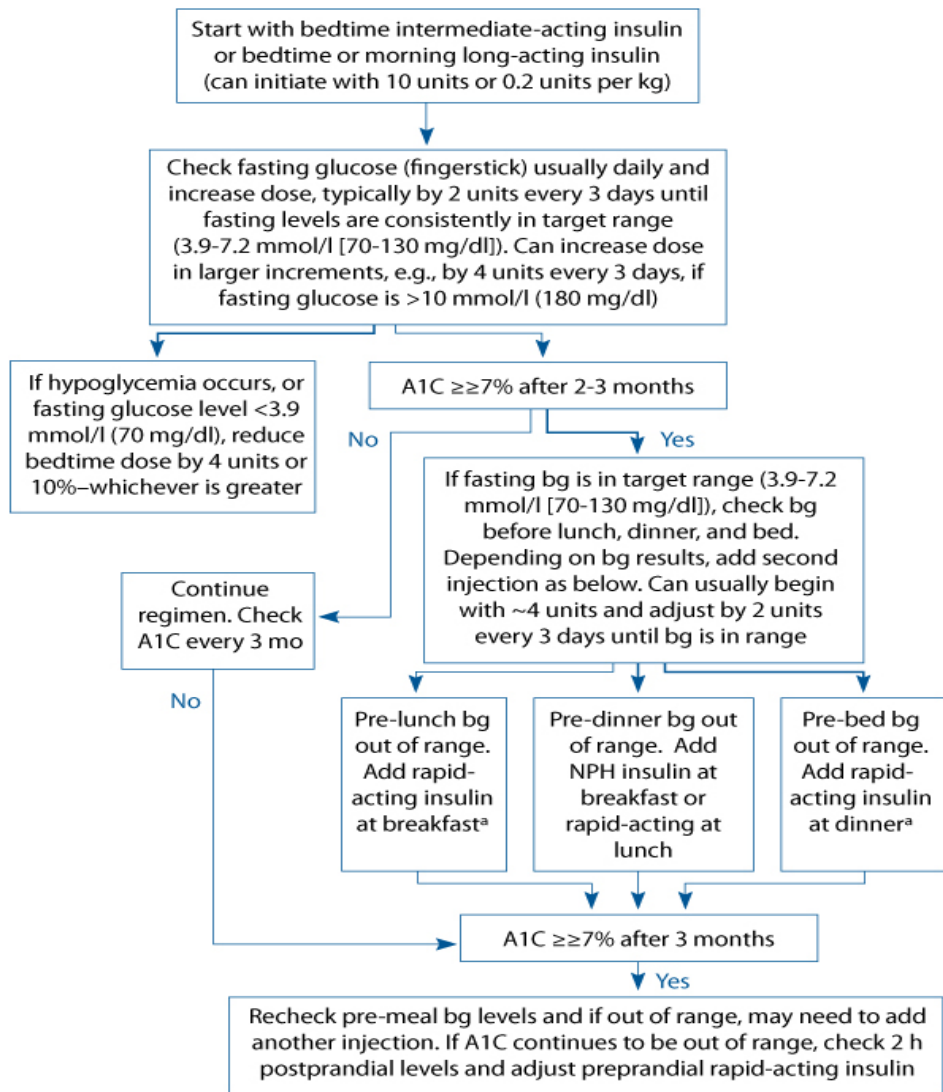
INSULIN DOSING FOR TYPE 1 DIABETES

- First choice: glargine + premeal regular insulin (rapid-acting analogues [lispro and aspart] are preferred because of improved glycemic control and decreased risk of hypoglycemia; administer 10-15 minutes before or immediately after meals)
- Second choice: NPH or detemir 2 times per day + premeal regular insulin (lispro or aspart preferred)
- Third choice: NPH 2 times per day or at night + regular insulin (lispro or aspart) TID; the patient must not miss meals
- Starting basal dosage is 0.6 units/kg per day, given as 1 dose of glargine or divided as 2 doses of NPH or detemir; adjust dosage based on SMBG
- Starting prandial dosage is 5-10 units given 10-15 minutes before or immediately after meals; adjust dosage based on SMBG





Initiation and Adjustment of Insulin Regimen

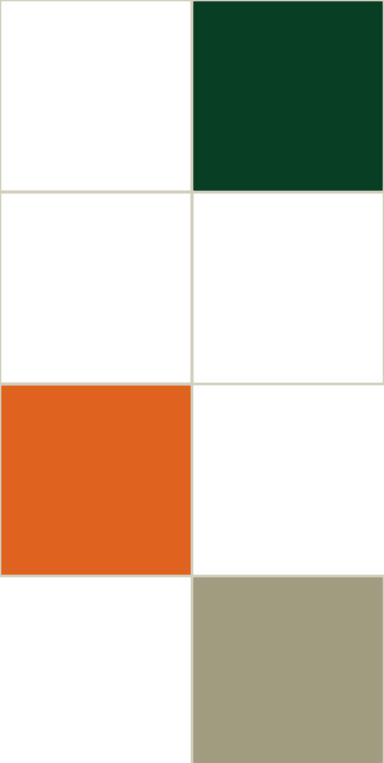


Other Therapies

Important for reduction of macrovascular disease, including CV events

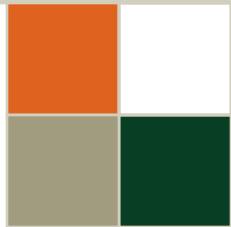
Intervention	Dosage	Comments
Aspirin	81 mg daily	<ul style="list-style-type: none"> •Recommended as secondary prevention for patients with a history of CV disease •Consider as primary prevention for patients aged ≥ 40 with type 2 diabetes and ≥ 1 other CV risk factors •Consider for patients aged 30-40 with type 2 diabetes and other CV risk factors, and for those with type 1 diabetes
Smoking cessation	N/A	<ul style="list-style-type: none"> •Assess readiness at each visit •Refer to cessation programs when patient is ready •Offer adjuncts as needed (eg, nicotine patches, bupropion) •See Smoking Cessation
ACE inhibitor or ARB	Varies by agent	<ul style="list-style-type: none"> •For treatment of microalbuminuria and hypertension in diabetic patients
Hydrochlorothiazide	25 mg daily	<ul style="list-style-type: none"> •For treatment of hypertension





Monitoring and Other Prevention Strategies

Method	Goal	Comments
HbA1c	<ul style="list-style-type: none"> •<7%; less-stringent control may be appropriate for patients with advanced microvascular disease, comorbidities, or short life expectancy 	<ul style="list-style-type: none"> •Every 3 months if not at goal or after change of medication or dosage •Every 6 months if at goal
SMBG	<ul style="list-style-type: none"> •Postprandial goal: <180 mg/dL (for type 2 diabetes) •Fasting goal: 90-130 mg/dL 	<ul style="list-style-type: none"> •Patients on insulin: measure 3 times daily before meals until glucose is controlled; then measure once daily alternating prebreakfast, lunch, supper, and bedtime •Midnight SMBG may be helpful to detect hypoglycemia if FBG is persistently elevated (from the dawn phenomenon [Somogyi effect]) •Patients not on insulin: if unstable or in poor glycemic control, measure fasting glucose several times per week, or on specified timeline; if controlled, measure 2 times/week •Patients should be educated regarding symptoms of hypoglycemia (eg, sweating, anxiety, disorientation, tachycardia) and instructed to ingest hard candy, juice, or other rapidly absorbed glucose source if symptoms occur •Note: SMBG has no benefit if not used to guide therapy



Blood pressure	<ul style="list-style-type: none"> •SBP: <140 mmHg •DBP: <80 mmHg 	<ul style="list-style-type: none"> •At each office visit. Treat if elevated. (see Hypertension)
Fasting lipids	<ul style="list-style-type: none"> •LDL: <100 mg/dL (<70 mg/dL with CV disease) •HDL: >40 mg/dL •TG: <150 mg/dL 	<ul style="list-style-type: none"> •Every 3-6 months if adjusting medications •Annually if stable and at goal •Use statins or other lipid-lowering agents as indicated •Be aware of possible interactions between PIs and statins (see Dyslipidemia and Lipid-Lowering Medications) •With most PIs, rosuvastatin or pravastatin is preferred; alternatively, low dosage of atorvastatin •May need to increase dosage when using statins with NNRTIs
LFTs	<ul style="list-style-type: none"> •ALT <2.5 times upper limit of normal 	<ul style="list-style-type: none"> •Monitor every 6 months in patients on sulfonyleureas or statins



Urine albumin/Cr ratio	<ul style="list-style-type: none"> •Slow progression of renal injury •Albumin/Cr ratio \leq30 mg/g 	<ul style="list-style-type: none"> •Microalbuminuria: urine albumin/Cr ratio $>$30 mg/g; confirmed with 2 out of 3 urine tests. Treat albuminuria with ACE inhibitor or ARB (see Renal Disease)
Foot examination	<ul style="list-style-type: none"> •Prevention of ulcers, infections •Detection of neuropathy •Early intervention 	<ul style="list-style-type: none"> •Perform foot risk assessment annually (see Initial Evaluation, above) •Educate patient about preventive foot care •Refer to Podiatry as needed for lesions and protective footwear •Refer to Vascular Surgery for evaluation of arterial insufficiency
Retinal eye examination	<ul style="list-style-type: none"> •Vision maintenance; early diagnosis of retinopathy 	<ul style="list-style-type: none"> •Annually, by an ophthalmologist •Laser therapy available for diabetic retinopathy
Influenza vaccine	<ul style="list-style-type: none"> •Decreased risk of infection 	<ul style="list-style-type: none"> •Annually
Pneumococcus vaccine	<ul style="list-style-type: none"> •Decreased risk of infection 	<ul style="list-style-type: none"> •Every 5 years
Counseling on diet, weight loss, and exercise	<ul style="list-style-type: none"> •Improved glycemic control 	<ul style="list-style-type: none"> •On diagnosis and at every visit



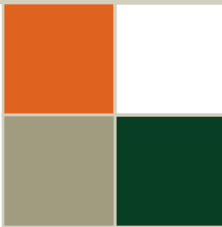
PATIENT'S EDUCATION

- ART can increase the risk of diabetes in some individuals. Patients should report any difficulty with excessive hunger and thirst and increased urination. Health care providers will monitor blood glucose when doing laboratory work, but it is important for the patient to report the presence of any symptoms.
- Review the patient's eating habits and explain the need to work with a dietitian to keep blood glucose (and triglycerides) within normal limits. Eating a proper diet can reduce the risk of permanent damage to the blood vessels of the eye, the kidney, and the brain, and it can reduce the risk of a heart attack.
- Emphasize other lifestyle modifications, such as weight loss (if appropriate).
- Encourage patients to get regular cardiovascular exercise; work with them to identify activities that might be realistic and acceptable for them.
- Provide medication-specific education, especially if the patient will be taking diabetes medications.
- Consider referral to a diabetes clinic for specialty needs.



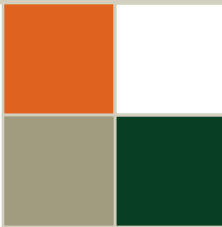
WHEN TO REFER

- Refer all patients with diabetes for education.
- All patients with Type 1 diabetes:
 - Should be referred to a diabetes clinic with multidisciplinary resources (eg, diabetologist, diabetes nurse, educator/manager, and registered dietitian) for institution and adjustment of insulin therapy.
 - If expeditious referral is not possible, the primary care provider should institute "survival" insulin therapy: see **Insulin dosing for Type 1 diabetes** under [Insulin Regimen Selection](#).



WHEN TO REFER

- Refer to Podiatry for foot lesions, ingrown toenails, foot deformities, or protective footwear.
- Refer to Vascular Surgery for evaluation of arterial insufficiency.
- Refer to Endocrinology for recurrent hypoglycemia or refractory hyperglycemia.
- Refer to an emergency department for patients suspected of diabetic ketoacidosis or nonketotic hyperglycemia based on orthostatic hypotension, tachycardia, disorientation, or ketotic breath.



SUMMARY



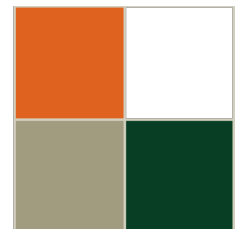
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THANK YOU



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