HIV and Comorbidities

Jennifer Janelle, MD
University of Florida College of Medicine, Gainesville

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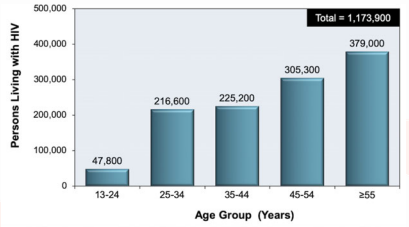
Objectives

1. Recognize chronic comorbid diseases that may occur in people with HIV (PWH)
2. Recommend interventions for modifiable risks for comorbid diseases in PWH

Persons with Diagnosed or Undiagnosed HIV, by Age Categories, United States 2018



*Estimate for persons ≥13 years of age living with diagnosed or undiagnosed HIV infection

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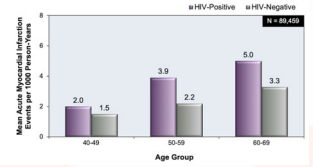
National HIV Curriculum. November 2020. Available at https://www.hiv.uw.edu/go/screening-diagnosis/epidemiology/core-concept/all#hiv-prevalence. Accessed 11.15.20.

HIV and Cardiovascular Disease

- Cohort studies suggest people with HIV have a 1.5 – 2 fold greater risk of cardiovascular disease than the general population

Veterans Aging Cohort Study, 2003-2009



National HIV Curriculum. November 2020. Available at https://www.hiv.uw.edu/go/screening-diagnosis/epidemiology/core-concept/all#hiv-prevalence. Accessed 11.15.20.

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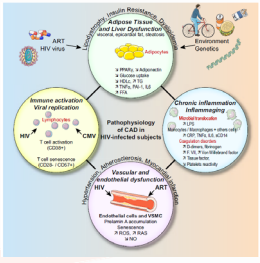
Risk Factors for Cardiovascular Disease in HIV



Boccara F, et al. J Am Coll Cardiol. 2013 Feb 5;61(5):511-23.

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Case

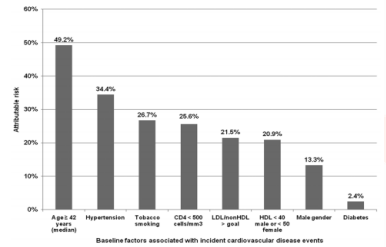
- 52 year old man presents to the emergency room with crushing substernal chest pain and is diagnosed with a heart attack
- He was diagnosed with HIV 12 years ago
  - Lowest CD4 count 40 cells/mm^3, highest HIV viral load 75,000 copies/mL
  - Current CD4 count 550 with HIV viral load <20 copies/mL
  - Current antiretroviral therapy (ART) Triumeq (abacavir, lamivudine and dolutegravir)
  - No other medications
  - + Smoker

Mentimeter

Of the following, which is associated with the highest relative risk for heart attack in this patient?

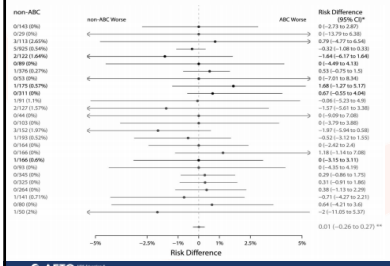
A. Cigarette smoking
B. Lipid level (LDL 180/HDL 30)
C. Abacavir use
D. HIV infection

Risk Factors For Cardiovascular Events: HIV Outpatient Study



Lichtenstein KA. Clin Infect Dis 2010;51(4):435-447.

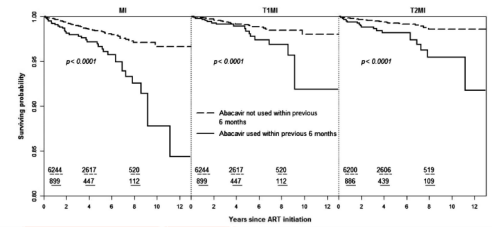
FDA Meta-Analysis: No Association Between Abacavir Use with MI



Risk difference 0.008% with 95% CI -0.26% to 0.27%

Ding, X, et al. J Acquir Immune Defic Syndr 2012;61:441-447.

Time from ART Initiation to First MI, by Recent Abacavir Use, NA-ACCORD.



Elion RA, et al. J Acquir Immune Defic Syndr. 2018 May 1;78(1):62-72.

Association Between HIV and Cardiovascular Disease

- Lower CD4 = higher MI risk
- HIV viremia and immune dysfunction = higher MI risk
- Even with sustained HIV viral suppression = higher MI risk
- PWH have a higher risk for strokes
- Women with HIV infection may be at particularly elevated risk
- Coinfection with HIV and hepatitis C may increase risk of stroke further
- Some ART may be associated with increased risk

Cardiovascular Risk Reduction in PWH

- Start ART as soon as possible after diagnosis
- Achieve and sustain suppressed HIV RNA levels
- Encourage smoking cessation
- Promote physical activity
- Manage lipid, blood pressure, or glycemic abnormalities
- Adhere to the ACC/AHA dietary guidelines
- Role of aspirin as primary prevention of CVD in PWH not well studied yet

National HIV Curriculum. November 2020. Available at https://www.hiv.uw.edu/go/screening-diagnosis/epidemiology/core-concept/all#hiv-prevalence. Accessed 11.15.20.

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Mentimeter

Which of the following is **false**?

A. HIV is now an independent ASCVD Risk enhancer
B. Validated CV risk assessment tools for use in PWH exist
C. Important drug interactions can exist between ART and statins
D. All PWH should be evaluated for ASCVD risk

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Risks for Cardiovascular Disease

- HIV is now a recognized independent ASCVD risk enhancer in the 2018 ACC/AHA multispecialty cholesterol management guidelines
  - No validated ASCVD risk assessment tools for PWH currently exist
    - Pooled cohort equations from the 2013 ACC/AHA guidelines
  - All patients should be assessed for ASCVD risk and evaluated and managed according to established guidelines

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Updated Primary Care Guidance: Lipids

- Recommendation 77
  - Lipid levels should be obtained prior to and within 1-3 months after starting ART. Patients with abnormal lipid levels should be managed according to the National Lipid Association Part 2 and 2018 Multispecialty Blood Cholesterol Guidelines

Thompson MA et al. Primary Care Guidance for Persons with HIV: 2020 Update. *Clinical Infectious Diseases*, ciaa1391, https://doi.org/10.1093/cid/ciaa1391
Published: 6 November 2020.

Case

Bernard is a 57 year old African American man diagnosed with HIV 10 years ago, new to your practice 3 months ago. When initially seen in your clinic, he was noted to have high cholesterol. Smoking cessation, exercise and heart healthy diet counseling were provided. He declined referral to the Tobacco Free Florida Quitline.

Social History: Smokes 1 pack of cigarettes daily. Drinks 6 beers daily.

ART: Genvoya (TAF/FTC/EVG/c)

PMH: Hypertension managed with lisinopril 20 mg daily

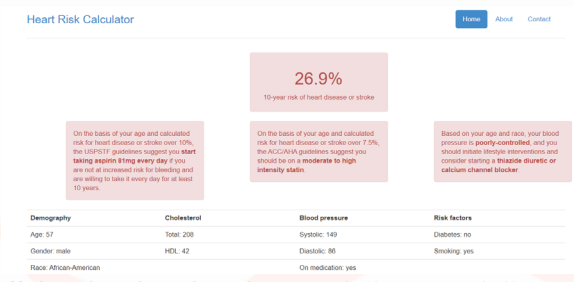
BP 149/86

Labs done 1 week ago: HIV RNA < 20 copies/mL CD4 count 545 cells/mm3

Lipids:

- Total cholesterol 208 mg/dL
- HDL: 42 mg/dL
- Trigs: 110 mg/dL
- LDL: 142 mg/dL

Remainder of labs were normal

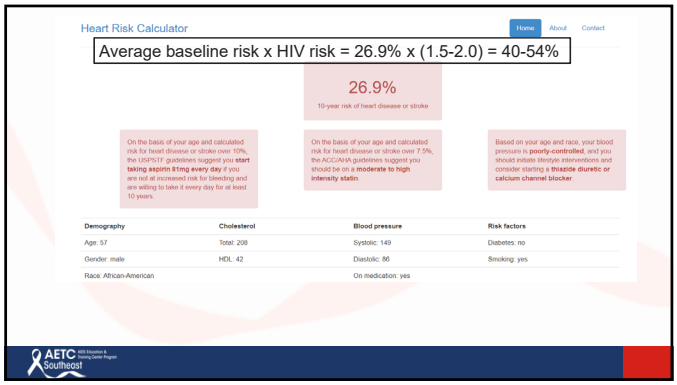


Moderate intensity statin may be atorvastatin 10mg, pravastatin 40mg, or simvastatin 20-40mg. **High intensity statin** may be atorvastatin 40mg-80mg

Mentimeter

What is the estimated fold change increased risk of cardiovascular events in people with HIV compared to those without HIV?

A. 5-6
B. 4-5
C. 10-12
D. 1.5-2



Mentimeter

Of the statin options listed below, which is contraindicated for use in Bernard given his current ART (Genvoya)?

A. Simvastatin 20 mg daily
B. Atorvastatin 10 mg daily
C. Pravastatin 40 mg daily

Table 5. Statin Interactions with ART[1,2]

Protease Inhibitor (PI) Interactions

NOTE: Interactions with indinavir, fosamprenavir, nelfinavir , saquinavir, and tipranavir are not included since these are rarely used

Statin	Interactive PI(s)	Prescribing Recommendation
Atorvastatin	ATV, ATV/r	Titrate atorvastatin dose carefully (editors of this resource usually would not exceed 20 mg daily)
	ATV/c	**Do not combine**
	DRV/c, DRV/r, LPV/r	Titrate atorvastatin dose carefully (not to exceed 20 mg daily)
Fluvastatin	All HIV PIs	No data available
Lovastatin Simvastatin	All HIV PIs	**CONTRAINDICATED**
Pitavastatin	All HIV PIs	No dosage adjustments necessary
Pravastatin	ATV/c, ATV/r, DRV/c or DRV/r	Titrate pravastatin dose carefully while monitoring for toxicities
	LPV/r	No dosage adjustments necessary
Rosuvastatin	ATV/r, ATV/c, LPV/r	Titrate rosuvastatin dose carefully (not to exceed 10 mg daily)
	DRV/c, DRV/r	Titrate rosuvastatin dose carefully (not to exceed 20 mg daily)

Stribild® (EVG/c/TDF/FTC) & Genvoya® (EVG/c/TAF/FTC) Interactions

Statin	Interacting Agent	Prescribing Recommendation
Atorvastatin	cobicistat	Titrate atorvastatin dose carefully (not to exceed 20 mg daily)
Fluvastatin Pitavastatin Pravastatin	cobicistat	No data or dosage recommendation
Lovastatin Simvastatin	cobicistat	**CONTRAINDICATED**
Rosuvastatin	cobicistat	Titrate rosuvastatin dose carefully (editors of this resource usually would not exceed 20 mg daily)

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ART in Adults & Adolescents Pocketcard. Available at seaetc.com.

Impact of Antiretroviral Medication on Lipids

Class	Impact on Lipids
NRTIs	• Stavudine > Zidovudine > Abacavir: ⇧TG and ⇧LDL • Tenofovir alafenamide: ⇧TG, ⇧LDL, ⇧HDL (no change in TC:HDL ratio) • Tenofovir DF has been associated with lower lipid levels than abacavir or tenofovir alafenamide
NNRTIs	• Efavirenz: ⇧TG, ⇧LDL, ⇧HDL
PIs	• All ritonavir- or cobicistat-boosted PIs: ⇧TG, ⇧LDL, ⇧HDL • Lopinavir-ritonavir and Fosamprenavir > Darunavir + Ritonavir and Atazanavir + Ritonavir: ⇧TG
INSTIs	• Elvitegravir-Cobicistat: ⇧TG, ⇧LDL, ⇧HDL
EIs	• N/A

Abbreviations: NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = nonnucleoside reverse transcriptase inhibitors; PIs = protease inhibitors; INSTIs = integrase strand transfer inhibitors; EIs = entry inhibitors

National HIV Curriculum. November 2020. Available at https://www.hiv.uw.edu/go/screening-diagnosis/epidemiology/core-concept/all#hiv-prevalence. Accessed 11.15.20.

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Diabetes and HIV

Table 2. Prevalence of Diabetes Mellitus Among 1278 Men at the Index Visit Between April and October 1999

Patient Group	Diabetes Mellitus* No. (%) of Patients	Diabetes Mellitus* PR (95% CI)†
Overall (N = 1278)	**101** (8)	NA
HIV seronegative (n = 710)	33 (5)	1
HIV infected not using HAART (n = 157)	11 (7)	2.21 (1.12-4.38)
HIV infected using HAART (n = 411)	57 (14)	4.64 (3.03-7.10)

Brown TT, et al. Arch Intern Med. *2005;165:1179-1184.*

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Diabetes and HIV

Random or fasting blood glucose and hemoglobin A1c should be obtained prior to starting ART. If random glucose is abnormal, fasting glucose should be obtained. After initiation of ART, only plasma glucose criteria should be used to diagnose diabetes. Patients with diabetes mellitus should have a HbA1c level monitored every 6 months with an HbA1c goal of <7%, in accordance with the American Diabetes Association Guidelines.

Thompson MA et al. Primary Care Guidance for Persons with HIV: 2020 Update. *Clinical Infectious Diseases*, ciaa1391, https://doi.org/10.1093/cid/ciaa1391
Published: 6 November 2020.

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HIV, Diabetes and Hemoglobin A1c

- In the general population, the diagnostic criteria for diabetes consists of:
  - Fasting plasma glucose ≥ 126 mg/dl or
  - 2-hour plasma glucose level ≥ 200 mg/dL during an oral glucose tolerance test conducted with a standard 75 g load or
  - HbA1c ≥ 6.5% or
  - If classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL
- However, studies have shown HbA1c may underestimate glycemia among PWH
  - American Diabetes Association (ADA) recommends AGAINST the use of HbA1c to diagnose diabetes in people with HIV on ART

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Diabetes Care 2019;42(Suppl. 1):S13–S28.

Diabetes and HIV

- Lifestyle modifications that include weight loss, increased exercise and dietary modifications
- If treatment needed, select hypoglycemic medications with insulin-sensitizing mechanism of action
- Treat according to ADA guidelines
- No evidence exists that switching ART is beneficial for impaired glucose tolerance

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Case

- 39 year old African American woman presents with newly diagnosed HIV infection. Tested as per routine by primary care doctor. She has no symptoms of HIV infection.
- CD4 150 cells/mm^3
- HIV viral load 250,000 copies/mL
- Other labs normal. ART started with Biktarvy (TAF/FTC/BIC)
- At 3 months follow-up visit
  - CD4 = 300 cells/mm^3
  - HIV viral load < 20 copies/mL

Mentimeter

Which of the following will most likely be present at her 3 month visit?

A. Skin rash
B. Mild cognitive impairment
C. Weight gain
D. Anemia

Clinical Infectious Diseases

MAJOR ARTICLE

Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials

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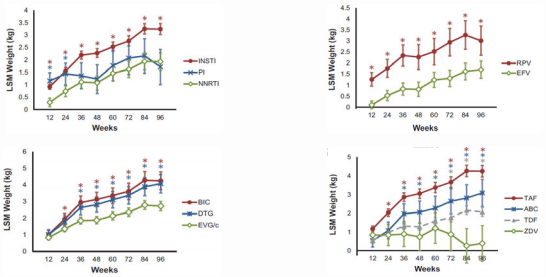
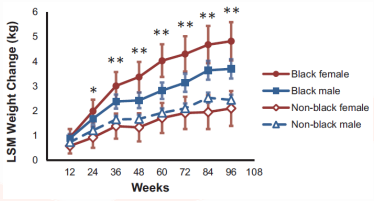
Weight Change in Participants Initiating ART



Sax PE, et al. Clin Infect Dis 2020:71(15 September) 1379.

Effect of Sex and Race on Weight Change in Individuals Initiating ART



Sax PE, et al. Clin Infect Dis 2020:71(15 September) 1379.

Table 3. Risk Factors for Any Weight Gain in Individuals Initiating Antiretroviral Therapy

Variable	Difference, kg	(95% CI)	*P* Value
CD4 count (<200 vs ≥200 cells/μL)	2.97	(2.81–3.13)	<.001
IV drug use (no vs yes)	1.41	(.97–1.85)	<.001
Race (black vs non-black)	0.99	(.87–1.11)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	0.96	(.84–1.08)	<.001
Symptomatic HIV (yes vs no)	0.51	(.36–.65)	<.001
Sex (female vs male)	0.23	(.07–.4)	.006
Age (<50 vs ≥50 y)	0.22	(.07–.37)	.004
BMI			
Obese vs normal	0.21	(.06–.36)	.005
Overweight vs normal	0.24	(–.36 to –.13)	<.001

Sax PE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis 2020:71(15 September) 1379.

Case

Ruby is a 45 year old African American woman who returns to clinic for follow-up. She was diagnosed with HIV infection 12 years ago when she had PCP pneumonia. Prior history of IV drug use – none since HIV diagnosis.

She has a history of hypertension, hepatitis C and hyperlipidemia.

ART consisted of Atripla (TDF/FTC/EFV) until 6 months ago when she was noted to have worsening renal function. ART was changed to Biktarvy (TAF/FTC/BIC).

HIV and Chronic Kidney Disease

- Risk factors in PWH
  - CD4 < 200 cells/mm^3
  - Elevated HIV RNA level
  - Black race
  - Older age
  - Female sex
  - Injection drug use
  - Diabetes, hypertension and hepatitis C
  - ART

Primary Care Guidance for PWH

- Complete blood count and chemistry panels should be monitored on a regular basis as needed to assess medication toxicity and to monitor potential or existing comorbid conditions (eg. Chronic kidney disease, hepatitis)
- Urinalysis should be monitored annually among those at risk for kidney disease
  - (Biannual testing is recommended for patients receiving tenofovir)

Thompson MA et al. Primary Care Guidance for Persons with HIV: 2020 Update. *Clinical Infectious Diseases*, ciaa1391, https://doi.org/10.1093/cid/ciaa1391
Published: 6 November 2020.

Mentimeter

Which antiretroviral medication(s) is/are associated with adverse kidney effects?

A. Tenofovir disoproxil fumarate
B. Atazanavir
C. Bictegravir
D. A&B

Case

- Robert is a 32 year old white man diagnosed with HIV 1 year ago diagnosed while in treatment for IV methamphetamine addiction.
- Also has chronic hepatitis B & C infection as a result of MSM sexual practices and IV drug use
- His provider started him on Biktarvy and strongly encouraged excellent medication adherence
- However, Robert recently relapsed into IV drug use and stopped his Biktarvy

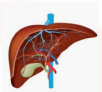
Mentimeter

Which of the following is NOT an expected outcome?

A. Flare of hepatitis B
B. Elevation of HIV viral load
C. Decrease in CD4 count
D. Improved liver enzymes

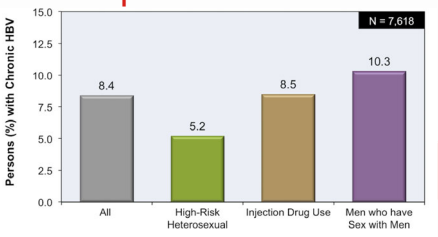
Regimens for HBV Coinfected Patients

- It is important to use two drugs that are active against hepatitis B in people with HIV infection and HBV coinfection
  - Tenofovir (TAF or TDF)
  - Emtricitabine (FTC) or lamivudine (3TC)
- Poor adherence or lapses in therapy in people with HBV can lead to severe liver disease including failure and death



Slide courtesy of Joanne Urban, Pharm D

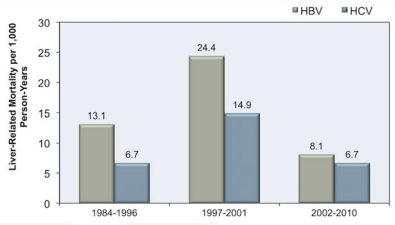
Hepatitis B and HIV



Chronic HBV Infection = HBsAg+ or detectable HBV DNA

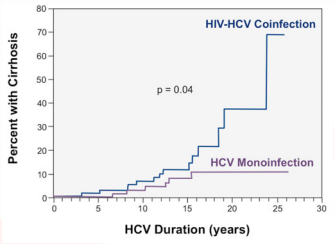
National HIV Curriculum. November 2020. Available at https://www.hiv.uw.edu/go/screening-diagnosis/epidemiology/core-concept/all#hiv-prevalence. Accessed 11.15.20.

Liver Related Mortality in PWH: Comparison Between HCV and HBV



National HIV Curriculum. November 2020. Available at https://www.hiv.uw.edu/go/screening-diagnosis/epidemiology/core-concept/all#hiv-prevalence. Accessed 11.15.20.

Comparison of Progression to Cirrhosis: HIV+HCV or HCV Mono-Infection



Hepatitis C Online. Available at https://www.hepatitisc.uw.edu/go/key-populations-situations/treatment-hiv-coinfection/core-concept/all. Accessed 11.19.20.

Treatment Efficacy: HIV-HCV vs HCV Mono-Infection

SVR Rates with GT 1 HCV-HIV Coinfection and HCV Monoinfection

Regimen (12 weeks)	Genotype 1			
	HCV-HIV Coinfection		HCV Monoinfection	
	Study	SVR	Study	SVR
Elbasvir-Grazoprevir	C-EDGE Coinfection	95%	C-EDGE TN	95%
Glecaprevir-Pibrentasvir	EXPEDITION-2	98%	ENDURANCE-1	99%
Ledipasvir-Sofosbuvir	ION-4	96%	ION-1	99%
Sofosbuvir-Velpatasvir	ASTRAL-5	95%	ASTRAL-1	98%

Hepatitis C Online. Available at https://www.hepatitisc.uw.edu/go/key-populations-situations/treatment-hiv-coinfection/core-concept/all. Accessed 11.19.20.

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Summary

- Given longer lifespan of PWH, need to evaluate and manage conditions associated with aging as higher risk in those with HIV
  - Cardiovascular disease
  - Renal and hepatic disease
  - Obesity/metabolic syndromes
- Many PWH have modifiable risk factors for co-morbidities
- All members of the care team have an important role in counseling and encouraging behavior changes that promote health

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