HIV and Metabolic Complications: Cardiovascular Diseases and Diabetes

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AUGUST 22, 2019
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Howard University
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CME Disclosures:
Planning Committee And Speaker

Howard University Caribbean Clinicians Community of Practice (CCCOP)
Planning Committee: The following committee members have nothing to disclose in relation to this activity:

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Marjorie Douglas

Speaker: The following speaker has nothing to disclose in relation to this activity: Vladimir Berthaud, MD, MPH, FACP, FIDSA, DTMH
**Intended Audience:** Health service providers: Physicians, Physician Assistants, Nurse Practitioners, Pharmacists, Dentists, Nurses, Social Workers, Case Managers and other Clinical Personnel.

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HIV and METABOLIC COMPLICATIONS: Cardiovascular Diseases and Diabetes
LEARNING OBJECTIVES

1. Discuss the potential mechanisms of cardiovascular disease in persons living with HIV
2. Describe common metabolic diseases in persons living with HIV and prescribe the recommended treatment modalities
3. Discuss the effectiveness of HIV treatment as secondary prevention
4. Define key Caribbean populations most impacted by HIV comorbidities
HIV EPIDEMIC AT A GLANCE: GLOBAL AND CARIBBEAN

Global

Caribbean
HIV PREVALENCE AMONG KEY POPULATIONS, CARIBBEAN 2015-2017

Source: 2018 Global AIDS Monitoring.
Nearly 90% of new infections occurred in
• Cuba,
• Dominican Republic,
• Haiti,
• Jamaica.

87% of AIDS-related deaths occurred in
• Dominican Republic,
• Haiti,
• Jamaica.
HIV TESTING AND TREATMENT CASCADE, CARIBBEAN 2017

Source: UNAIDS special analysis, 2018; see annex on methods for more details.
CASE PRESENTATION
CASE PRESENTATION

35-year-old man diagnosed HIV+ in 2000

- PMH: acute hepatitis A
- Herpes zoster
- Peripheral neuropathy
- Secondary syphilis/Neurosyphilis
- Asthma
- Hypertension
- Hyperlipidemia
- DVT/recurrent pulmonary embolism
- Peripheral vascular disease
- GERD/duodenal ulcer
- Acute anterior wall myocardial infarction with PCI
- Congestive heart failure
- Lymphoma
- Osteopenia
EVOLUTION OF HIV LANDSCAPE

- Marked reduction in opportunistic infections and HIV-related mortality
- Effectiveness of HIV treatment as secondary prevention
- Persistent inflammatory state and reservoirs
- Increased incidence of comorbidities
- Treatment setting shifting from inpatient to outpatient to community
- Pervasive stigma and discrimination
COMORBIDITIES OCCUR AT SIMILAR AGE BUT INCREASED FREQUENCY IN HIV-POSITIVE PATIENTS

Subanalysis of Veteran’s Aging Cohort Study
Risk of age-related outcomes (MI, ESRD, non-AIDS defining cancers) by HIV status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Mean Difference in Age, Yrs</th>
<th>Risk aIRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>-0.04 (-0.62 to 0.54)</td>
<td>1.81 (1.49-2.20)</td>
</tr>
<tr>
<td>ESRD</td>
<td>-0.23 (-0.69 to 0.23)</td>
<td>1.43 (1.22-1.66)</td>
</tr>
<tr>
<td>HIV-associated cancers*</td>
<td>-0.57 (-0.93 to -0.21)</td>
<td>1.84 (1.62-2.09)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>-0.45 (-0.78 to -0.12)</td>
<td>0.95 (0.85-1.06)</td>
</tr>
</tbody>
</table>

- Higher rate of MI, ESRD, HIV-associated cancers vs. HIV-uninfected adults
- HIV-associated cancer diagnoses occurred ~ 7 months earlier in HIV-infected adults vs. HIV-uninfected adults


* Included anal, Hodgkin’s lymphoma, liver, lung, oral cavity, and pharynx.
2,159 HIV+ patients at 11 clinics in 4 countries

37.7% had >1 NCD
(ARR, 1.42; 95% CI, 1.22-1.66)

66% on ART:
(ARR, 1.50; 95% CI, 1.27-1.78) for VS
(ARR, 1.38, 95% CI, 1.13-1.68) for non-VS

Nadir CD4 <200:
(ARR, 1.43; 95% CI, 1.06-1.93)

ART was independently associated with
dysglycemia and hypercholesterolemia
OVERVIEW OF CHRONIC DISEASE IN THE CARIBBEAN
Chronic diseases contribute to almost 50% of disability-adjusted life years lost.

Treatment of hypertension and diabetes in selected Caribbean countries (Bahamas, Jamaica, Barbados, and Trinidad and Tobago) are estimated to consume a range of 1.4 to 8.0% of GDP.

Heart disease, stroke, cancer, diabetes are the main causes of death in the Caribbean. (Increased diabetes prevalence rates as high as 10%)

Hypertension is one of the most important risk factors for heart disease and has been shown to affect 22.6%, 25.8% and 27.0% of the population in Jamaica, St. Lucia and Barbados respectively.

Obesity and overweight is an ever-increasing concern throughout the Caribbean.

In Barbados 1/3 men and 3/5 of women are overweight, Incidence of obesity for men is 9% and that for women 13.1%.
OVERVIEW OF CHRONIC DISEASE IN THE CARIBBEAN

Source: Personal communication from Colin Mather to George Alleyne.
Prospective cohort study of 816 HIV+ adults, randomized to early (N = 408) versus delayed initiation of ART (when CD4 <200 or AIDS-defining condition; N = 408)

To determine how baseline BP and incident hypertension (HTN) related to ART initiation, HIV-related inflammation, and mortality

Median follow-up time: 7.3 years

Median age at enrollment: 39 years
HYPERTENSION AND MORTALITY IN HIV-INFECTED ADULTS IN HAITI

- Similar incidence of HTN, 3.41 per 100 person years in both groups

- Independent predictors: older age, higher BMI, and plasma IL-6 levels (adjusted HR = 1.23, p <0.001)

- Systolic BP >140mmHg at enrollment and systolic pressure <90mmHg associated with increased mortality (aHR = 2.25, p = 0.04)

- Prevalent and incident hypertension also significantly associated with mortality
KAPLAN-MEIER ESTIMATES FOR SURVIVAL BY SYSTOLIC BLOOD PRESSURE MEASUREMENT

Graph A: Probability of survival over years from enrollment for normal and high systolic blood pressure (SBP) groups. The p-value is 0.03 by log-rank test.

Graph B: Probability of survival over years from enrollment for normal and low SBP groups. The p-value is 0.045 by log-rank test.

Legend:
- Normal SBP
- High SBP
- Low SBP

Number at risk:
- Normal SBP: 741, 646, 596, 536, 259
- High SBP: 29, 24, 17, 13, 6
- Low SBP: 741, 646, 596, 536, 259
HIV DISEASE PROGRESSION
End-stage liver disease is strongly associated with:

- Immunodeficiency
- Hepatitis C infection
- Chronic hepatitis B infection
Chronic hepatitis C infection is associated with:

- Coronary artery disease
- Diabetes mellitus
- Osteoporosis
- Hypogonadism
- Renal insufficiency
HIV DISEASE PROGRESSION

- Increasing age associated with higher risk of chronic kidney disease
- Higher risk of progression to ESRD in patients with HIV-associated nephropathy
- African American race is a strong risk factor
FACTORS IMPLICATED IN PERSISTENT INFLAMMATION AND IMMUNE ACTIVATION IN HIV PATIENTS

- Residual HIV replication
- Antiretroviral drugs
- Established vascular damage
- Chronic coinfections
- Bacterial translocation
- Homeostatic drive
HIV DISEASE PROGRESSION

- Cardiovascular disease (CVD):
  - Intermittent antiretroviral therapy is associated with higher rate of CVD
  - Suggestive effect of viremia on endothelium vasculature, leading to increased tissue factors and initiation of coagulation cascade
  - In elderly HIV positive men, vascular response to endothelium dependent vasodilator is significantly blunted
CARDIOVASCULAR DISEASE (CVD) CUMULATIVE INCIDENCE CURVES FOR MALES AND FEMALES
CARDIOVASCULAR DISEASE IN PLWH

- Essential hypertension
- Peripheral vascular disease
- Coronary heart disease
- Congestive heart failure
- Stroke
- Kidney failure
- Thromboembolic disease
Circulating concentrations of endothelial-, platelet-, monocyte-, and leukocyte-derived microparticles are higher in antiretroviral-treated HIV-1-seropositive men and adversely affect endothelial cells promoting cellular inflammation, oxidative stress, senescence, and apoptosis.

Circulating microparticles may contribute to the vascular risk associated with HIV-1 infection.

- Hijmans JG, Stockelman KA, Garcia V, et al.

Circulating microparticles are elevated in treated HIV-1 infection and are deleterious to endothelial cell function.

- J Am Heart Assoc. 2019
The Multicenter AIDS Cohort Study (MACS) of men and the Women’s Interagency HIV Study (WIHS) evaluated the associations between specific macrophage-associated inflammatory markers measured once in middle age and incident carotid artery plaque development.

4 markers of macrophage activation & associated inflammation, soluble CD14 (sCD14), soluble CD163 (sCD163), galectin-3-binding protein, and galectin-3, were associated with HIV+ status.

sCD14 was consistently associated with incident carotid plaque formation over 7 years, even after adjustment for demographic, behavioral, and cardiometabolic factors, as well as C-reactive protein (CRP), and interleukin-6 (IL-6).
Additionally, sCD14 marginally improved the ability of a risk prediction model incorporating traditional cardiovascular risk factors, CRP, and IL-6 to discriminate risk for incident carotid plaque development. 


Association of macrophage inflammation biomarkers with progression of subclinical carotid artery atherosclerosis in HIV-infected women and men.

J Infect Dis. 2017; 1352-61
## CARDIOVASCULAR EFFECTS OF ART DRUGS

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Cardiovascular Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Abacavir, tenofovir, lamivudine, emtricitabine, emtricitabine, zidovudine</td>
<td>Direct effect on mitochondrial enzymes, inhibition of nucleoside transport, inhibition of nucleoside phosphorylation and generation of reactive oxygen species in the mitochondria</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Efavirenz, etravirine, nevirapine, rilpivirine</td>
<td>Pharmacological interaction with other classes of drugs (calcium channel blockers, warfarin, beta-adrenoceptor antagonists, nifedipine, quinidine, and theophylline)</td>
</tr>
<tr>
<td>ISTI</td>
<td>Raltegravir</td>
<td>No specific side effects or drug interactions</td>
</tr>
<tr>
<td>PI</td>
<td>Atazanavir, fosamprenavir, darunavir, ritonavir</td>
<td>Induction of dyslipidemia by mediating the expression of proinflammatory cytokines, increasing apoptosis and reduced proliferation of peripheral adipocytes, contributing to biosynthesis of triglycerides in the liver, and promoting insulin resistance and lipodystrophy</td>
</tr>
</tbody>
</table>
# ART Drugs and Related Cardiovascular Effects

<table>
<thead>
<tr>
<th>Statins</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent: Insomnia, headache, GI symptoms, hepatitis, myalgia, and myositis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare: Rhabdomyolysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Use with PIs</strong></td>
<td>No dose change</td>
<td>No dose change</td>
<td>Contraindicated</td>
<td>No dose change</td>
<td>Lower dose</td>
<td>Contraindicated</td>
</tr>
<tr>
<td><strong>Use with NNRTIs</strong></td>
<td>Lower dose</td>
<td>No dose change</td>
<td>No dose change</td>
<td>No dose change</td>
<td>Lower dose</td>
<td>No dose change</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Second choice</td>
<td>Higher risk of myopathy and rhabdomyolysis with PIs</td>
<td>First choice</td>
<td>Contraindicated with boosted atazanavir and lopinavir</td>
<td>Higher risk of myopathy and rhabdomyolysis with PIs</td>
<td></td>
</tr>
</tbody>
</table>
EXAMPLE OF ADVERSE CARDIOVASCULAR EFFECTS
Alteration of endocrine glandular function:

- At the onset of the HIV epidemic, glandular involvement with opportunistic infections and malignancies was the primary mechanism.

- In the era of potent ART, endocrine dysfunction results mainly from direct effect of HIV viral proteins, through generation of local and systemic cytokines and inflammatory response.
### ADA Definition of Diabetes and Prediabetes

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin A1c</th>
<th>Fasting Plasma Glucose</th>
<th>Random Plasma Glucose</th>
<th>Oral Glucose Tolerance Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>≥6.5%</td>
<td>≥126 mg/dL (≥7.0 mmol/L)</td>
<td>≥200 mg/dL (≥11.1 mmol/L) with polyuria and polydipsia</td>
<td>≥200 mg/dL (≥11.1 mmol/L)</td>
</tr>
<tr>
<td><strong>Prediabetes</strong></td>
<td>5.7%–6.4%</td>
<td>100–125 mg/dL (5.6–6.9 mmol/L)</td>
<td>...</td>
<td>140–199 mg/dL (7.8–11.1 mmol/L)</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>&lt;5.7%</td>
<td>≤99 mg/dL (≤5.5 mmol/L)</td>
<td>...</td>
<td>≤139 mg/dL (≤7.7 mmol/L)</td>
</tr>
</tbody>
</table>
COMMON METABOLIC DISEASES AND HIV

- Bone disorders
- Gonadal dysfunction
- Adrenal insufficiency
- Thyroid dysfunction
- Lipodystrophy, lipoatrophy and lipohypertrophy
- Dyslipidemia
- Diabetes mellitus
Lipodystrophy, lipoatrophy and lipohypertrophy or
Fat redistribution: visceral obesity and ectopic fat accumulation
- Due to dysfunctional fibrotic subcutaneous adipose tissue
- Promotes insulin resistance
- Basal, mean overnight growth hormone concentrations, and growth hormone pulse amplitude are low
- Growth hormone pulse frequency and growth hormone pulse amplitude remain normal

HIV affects immune cell trafficking into the adipose compartments, with effects on adipogenesis, lipolysis, and ectopic fat accumulation
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Name</th>
<th>Special Considerations in HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incretins</td>
<td>Increase glucose-dependent insulin secretion Decrease inappropriate glucagon secretion Increase β-cell growth/replication Slow gastric emptying</td>
<td>Liraglutide</td>
<td>Gliptins have molecular targets on immune cells; no evidence of changes in CD4 or VL Saxagliptin interacts with strong CYP3A4/5 inhibitors (RTV); reduce saxagliptin dose</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td></td>
<td>Exenatide</td>
<td></td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Increase insulin synthesis and release from pancreatic β-cells Decrease glucagon secretion from pancreatic α cells Decreased glucagon secretion results in decreased hepatic glucose production</td>
<td>Sitagliptin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saxagliptin</td>
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<td></td>
<td></td>
<td>Vildagliptin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Linagliptin</td>
<td></td>
</tr>
<tr>
<td>Gliptins</td>
<td>Reduce reabsorption of filtered glucose from the tubular lumen &amp; lower the renal threshold for glucose Increase urinary excretion of glucose</td>
<td>Dapaglifozin</td>
<td>Consider increasing the dose to 300mg if UGT enzyme inducers (RTV) are administered with canagliflozin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Canaglifozin</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Stimulate insulin release from pancreatic β-cells</td>
<td>Repaglinide</td>
<td>Levels may increase when used with CYP3A4/CYP2C8 inhibitors (many PIs); EFV and ETR may increase nateglinide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nateglinide</td>
<td></td>
</tr>
</tbody>
</table>
Prevention of Microvascular Complications in Patients With Diabetes Mellitus

- **Target Area**
  - Retinopathy
  - Nephropathy
  - Neuropathy

- **Recommendation**
  - Yearly ophthalmologic exam
  - Optimize blood pressure and lipid control
  - Spot urine microalbumin every six months to screen for nephropathy
  - ACE inhibitor/ARB in patients with hypertension or microalbuminuria
  - Foot exams every 6–12 months
  - Instruction in foot care
  - Referral to podiatry if evidence of neuropathy

*Clinical Infectious Diseases 2015;60(3):453–62*
CONCLUSION

- Strong evidence suggests that HIV plays a significant role in cardiovascular disease progression but underlying mechanisms are complex and incompletely understood.

- We need to better comprehend the interaction between traditional CVD risk factors (obesity, aging, and smoking, cocaine, HTN, DM, and dyslipidemia), ART and HIV.

- As HIV management faces more challenges due to aging and incident comorbidities, patient-centered multispecialty practice could replace the traditional care model of HIV specialty clinic.

- Further studies are underway to clarify the role of cellular, molecular, microbial, and inflammatory factors in the excess risk of cardiovascular disease among PLWH.
Thank You
TEST YOUR KNOWLEDGE
POST - TEST
Test Your Knowledge
Question #5

According to HCC, the leading causes of premature death in the Caribbean are: - please choose one

A. Stroke, diabetes, AIDS, and cancer
B. AIDS, heart disease, cancer, and hypertension
C. Heart disease, stroke, cancer, and diabetes
D. COPD, hypertension, renal failure, and heart disease
Test Your Knowledge
Question #6

Intermittent antiretroviral therapy is associated with a higher rate of CVD:

A. True
B. False
Test Your Knowledge
Question #7

In the era of potent ART, endocrine dysfunction results mainly from indirect
effect of HIV viral proteins, through generation of local and systemic
cytokines and inflammatory response:

A. True
B. False
Test Your Knowledge
Question #8

Common metabolic disease seen in HIV includes all except:

A. Bone disorders
B. Gonadal dysfunction
C. Thyroid dysfunction
D. Phenylketonuria (PKU)
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