Learning Objectives

After attending this presentation, participants will be able to:

- Identify mechanisms driving end organ disease in treated HIV
- Describe the effects of HIV infection on the intestinal microbiome
- Describe to patients the link between gut microbiome and a person’s overall health
ART Utilization And Viral Suppression

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>All Patients seen in last 12 months</td>
<td>1880</td>
<td>1894</td>
<td>1870</td>
<td>2475</td>
<td>2752</td>
<td>3016</td>
<td>3092</td>
</tr>
<tr>
<td>Recorded CD4 in last 6 months</td>
<td>1512 (86%)</td>
<td>1317 (91%)</td>
<td>1620 (97%)</td>
<td>2126 (88%)</td>
<td>2469 (83%)</td>
<td>2497 (73%)</td>
<td>2270 (71%)</td>
</tr>
<tr>
<td>Receiving ART</td>
<td>1683 (86%)</td>
<td>1692 (99%)</td>
<td>1607 (97%)</td>
<td>2356 (83%)</td>
<td>2599 (83%)</td>
<td>2851 (87%)</td>
<td>2663 (86%)</td>
</tr>
<tr>
<td>HIV L. &lt; 1000</td>
<td>1486 (80%)</td>
<td>1315 (80%)</td>
<td>1688 (83%)</td>
<td>2108 (81%)</td>
<td>2313 (81%)</td>
<td>2574 (80%)</td>
<td>2661 (87%)</td>
</tr>
<tr>
<td>HIV L. = 50</td>
<td>1030 (61%)</td>
<td>1048 (62%)</td>
<td>1347 (78%)</td>
<td>2036 (78%)</td>
<td>2310 (78%)</td>
<td>2397 (80%)</td>
<td>2270 (67%)</td>
</tr>
</tbody>
</table>

165 persons not prescribed ART
CD4 = 000: 165 (64%)
CD4 = 50-100: 62 (24%)
CD4 = 101-150: 22 (11%)
CD4 = 151-200: 18 (11%)
CD4 = 201-300: 7 (4%)
CD4 > 300: 7 (4%)

AGING
Chronic HIV Infection
ART Toxicity
HCV and other Co-infections
Obesity, Exercise, Diet, Smoking
Decreased Physical Functioning
Inflammation & Fibrosis
Dyslipidemia
Insulin Resistance
END ORGAN DISEASE

Emergence of Non-AIDS Comorbidities

Warriner AH et al. ID Clin N Am. 2014
What Is The Gut Microbiome, Alex?

- Large, stable community of bacteria
- ~100 trillion microbial cells
- ~1,000 bacterial species
- Unique to each individual
- Role in nutrient metabolism, barrier function & immunity
- Impacted by diet, genes, alcohol, tobacco, exercise, medications, stress

Four Major Phyla of Intestinal Microbiota

Further Breakdown of the Intestinal Microbiota
**Evolution of the Gut Microbiome**

- Year 0-3
  - Dynamic changes in flora
  - Highly adapted community established
- Homeostasis ensues
  - Stable adult microbiome
- Environmental factors cause stress
  - Induce dysbiosis
  - Influence human diseases
- With aging, the microbiome may degenerate
  - State of dysbiosis
    - Chronic inflammation
    - Immune senescence

**Microbiome Dysbiosis for 200, Alex?**

- The bacteria in the microbiome are symbiotic to the human organism and contribute to health and wellness.
- 4 predominate bacterial phyla
  - Firmicutes
  - Bacteroidetes
  - Actinobacteria
  - Proteobacteria
- Involved in many processes
  - Immune system development
  - Digestion and detoxification
  - Synthesis of vitamins
  - Hydrolysis of indigestible dietary compounds
  - Poly saccharides
  - Defense against pathogenic bacteria
  - Fat storage
  - Angiogenesis development
  - Behavior development

**Inflammatory Bowel Disease: Gut Dysbiosis in the Extreme!**

- The Triumvirate of Badness!
  - Microbial Dysbiosis
  - Loss of Barrier Function
  - Immune Dysfunction and Systemic Inflammation
What's All the Fuss About the Microbiome?

Wednesday, August 24, 2016

Slide 17 of 29

This is all very familiar
Look at guts of HIV!

Figure courtesy of Dr. Zdenek Hel.

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Improving Survival
But still below general population

Survival from age 27 years in 3499

Population controls
HIV: 2000-2005
Control ART
HIV: 2001-1999
Early ART
But still below general population

Slide 19 of 29

Comorbidity in relation to age

HIV-negative HIV-positive

[Graph showing the percentage of comorbidity in relation to age for HIV-negative and HIV-positive individuals.]
**Increasing Non-AIDS Comorbidities 2007-2013**

- 41,419 HIV patients
  - 31,229 from Commercial Insurance
  - 10,190 from Medicaid

**Common Comorbidities**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Commercial Insurance</th>
<th>Medicaid</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>43%</td>
<td>55%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>41%</td>
<td>46%</td>
</tr>
<tr>
<td>Diabeteis</td>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>OAD</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>CVD event</td>
<td>6%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Impact of HIV on CVD risk comparable to traditional risk factors including HTN, DM and hyperlipidemia.*

**CVD Prevalence and Incidence**


**Inflammation**

- ↑ Monocyte activation
- ↑ T cell activation
- ↑ Dyslipidemia
- ↑ Hypercoagulation

**Co-morbidities**

- Aging
- Hepatic steatosis and inflammation
- Metabolic syndrome
- Microbial translocation

**Loss of regulatory cells**

- CMV
- Excess pathogens

**HIV production**

- HIV replication

**HIV-associated fat**

- Metabolic syndrome

**Persistent Viral Infections are Bad**

- The majority of viral infections are cleared but
- Certain viruses may cause persistent infections.

**Two flavors of chronic persistent infections:**

- **True Latency** - the virus remains completely latent following primary infection e.g. HSV, VZV.
  - Its genome may be integrated into the cellular genome or exists as episomes.
  - Reactivation occurs with immunosenescence or stressor.

- **Persistence** - the virus replicates continuously in the body at a very low level e.g. HIV, HBV, CMV, EBV.
  - Induces T cell activation and exhaustion
  - Indirectly induce end organ disease → failure of adaptive immune response to clear pathogens
Dysfunctional Gut-Liver Axis Induces Systemic Inflammation

**HIV Infection Induced Changes in the GI Tract**
- Depletion of Th17, Th22 CD4 cells
- Dysbiotic intestinal flora
- Increased mucosal permeability

Consequent bacterial translocation via portal vein
- Activation of Intestinal Immune System
- Intrahepatic inflammation

**Intrahepatic Complications**
- Recruitment of Monocytes and Neutrophils
- Activation of Kupffer Cells
- Fibrogenesis

**Systemic Complications**
- Pre-inflammatory cytokines
- Insulin Resistance
- Activated Monocytes

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Dysbiosis in HIV infection

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An altered intestinal mucosal microbiome in HIV-1 infection is associated with mucosal and systemic immune activation and endotoxemia
Factors that need further understanding?

- Interaction between HIV, microbiome, and chronic diseases
- Role of diet in the setting of HIV
- Behavioral factors
  - Sexual practices
  - Exercise/sedentary lifestyle
  - Tobacco and Alcohol
- Potential interventions
  - Antibiotics
  - Probiotics/Prebiotics
  - Dietary supplements
  - Anti-inflammatory agents

How to Beat Inflammation

- Treat early!
- Continue ART
  - Maintain undetectable viremia
- Stop smoking
- Maintain normal weight
- If overweight, lose at least 5-10% of body weight
- Exercise
- Have a healthy diet
- Cut down on alcohol, avoid drugs
- Consider lipid lowering therapy (aka statins)
Conclusions

- HIV depletes the CD4 cells, preferentially from the gut-associated lymphoid system.
  - This alteration leads to impairment of the gut mucosa integrity.
  - This alteration also contributes to intestinal dysbiosis.
- Microbial translocation subsequently ensues with resultant systemic inflammation.
- Ultimately, this process leads to excess risk of many non-AIDS comorbidities.
- Diet and behavioral factors also contribute to this process.
- Studies are ongoing to identify interventions to reverse the alterations in the GALT, restore the intestinal mucosal health, and prevent the consequences of excess microbial translocation.

SUGGESTED READINGS


