HIV Associated Diarrhea: 2019

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Proud Member, MWAETC Echo Family

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Disclosures

Sadly, none

HIV Associated Diarrhea: 2019

- History and Epidemiology
- Etiology
  - HIV itself
  - Infectious pathogens
  - Non-infectious causes
- Diagnostic approach
- Treatment and recommendations

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History and Epidemiology

- Pre-ART era
  - Even before HIV was discovered the disease was known as slim disease in Africa, in part because of unremitting diarrhea
  - 70-100% of HIV+ patients reported frequent or chronic diarrhea
- ART era
  - 28-70% of patients report chronic diarrhea
  - From prescribing data 28% of patients on ART c/o chronic diarrhea

	Pre-ART era	ART era
Infectious	53%	13%
Non-infectious	32%	70%

(Call Am J Gastro 2000; Harding Sex Trans Infec 2010, Siddiqui J Clin Gastro 2007, Clay Infect Dis Ther 2014)

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History and Epidemiology

Study	Study details	Key finding
Call, Am J Gastro 2014	Retrospective 1995-97 N = 1757	Infectious: 53%-→13% Non infectious 32%-→ 70%
Knox, Am J Gastro 2000	Retrospective 1996-7 N = 671	Diarrhea 39%
Zingmond JAIDS 2003	Two X sectional cohorts (1996-2000) N = 3745	Diarrhea 53%
Siddiqui J Clin Gastro 2007	Prospective study 2002-03 N = 416	Diarrhea 28% (HIV+) Vs 7% (HIV-)
DaCosta DiBonaventura AIDS Care 2012	X sectional of patients on ART 2008 N = 953	ART related diarrhea 63%

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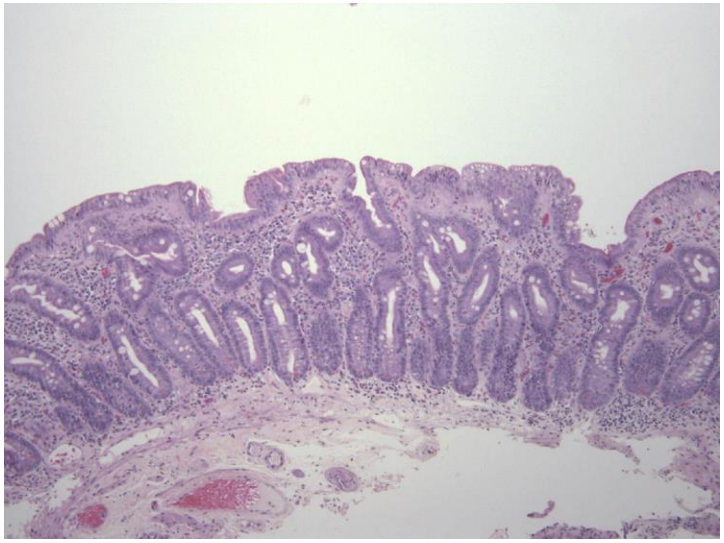
Etiology: HIV

- HIV Enteropathy
  - Can occur at any stage of HIV although more common in those with advanced, untreated HIV
  - Pathogenesis:
    - Profound depletion of gut-associated CD4 cells, especially CD4-TH-17 subset (involved in epithelial cell repair)
    - Increase in activated CD8 cells – promotes inflammation
    - Leading to gut leakage, bacterial translocation and malabsorption
  - Histologically: crypt cell proliferation → encroaches on villi → atrophy of villi
  - Clinically: malabsorption, weight loss



Note:
Blunted villi
Distorted crypts
Influx of lymphocytes

(Cello and Day Gastoenterology 2009)

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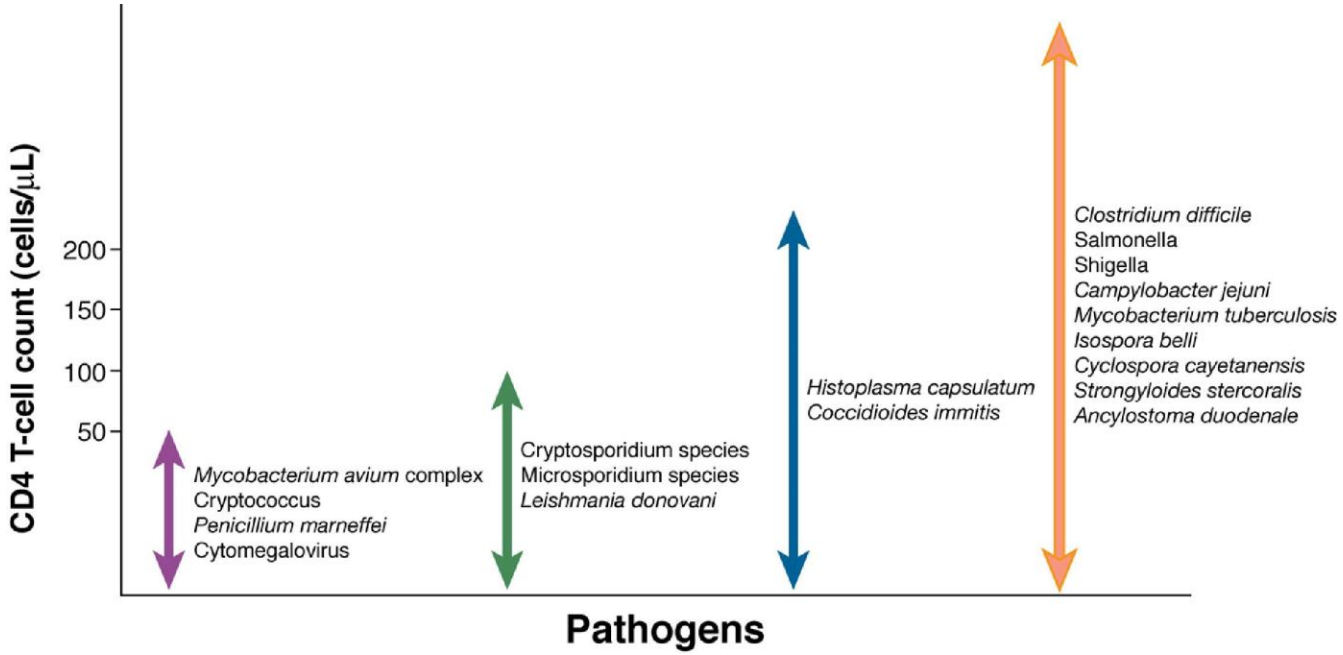
Etiology: Infectious Pathogens

- Bacteria
- Protozoa
- Fungi
- Viruses



(Cello and Day Gastroenterology 2009

Etiology: Bacteria

- *Campylobacter* spp.: (small bowel) a common cause of bacteremia in the pre-ART era
- *Salmonella* spp: (small bowel) common cause of bacteremia in the pre-ART, pre-TMP/SMX era. More common now in advanced, untreated HIV, especially in Africa and Russia.
- *Shigella* spp and pathogenic *E coli* (same organism?) (colon)
  - Now an STI
  - Outbreaks in Asia, Europe, North America
  - UK study: 2003-15: 20% of all non-travel related cases occurred in HIV+ (Vs 3% of travel-associated cases), 93% were men and 98% MSM. Highly associated with condomless sex
  - Often macrolide resistant – likely due to azithromycin exposure for the treatment of STIs

(Baker Lancet ID 2015, Krones Gastrointest Clin N Am, 2012)

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Etiology: Bacteria

- Gastroenteritis in MSM in Seattle (majority HIV+)
  - Cohort study of 235 MSM underwent stool pcr testing (January 2017-June 2018)
  - Testing was positive in 151/268 (episodes) = 60%

Pathogen	Percent detected
Bacteria	88.7%
E coli	33.1%
Shigella	30.5%
Campylobacter	17.2%
Parasite	40%
Giardia	20.5%
Cryptosporidia	6%
Virus (mostly norovirus)	26%

  - Resistance:
    - *Shigella* (19 isolates) all R to ampicillin and TMPSMX, 17/19 resistant to azithromycin, 1/19 R to cipro
    - *Campylobacter* (9 isolates): 7/9 R to cipro, 8/9 R to erythromycin

(Newman, Snoeyenbos-Newman, Cybulski, Fang CID 2019)

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Etiology: Bacteria

- LGV: procto-colitis: (rectum) More common in Africa, SEA, India and South America > North America and Europe.
  - Sharp rise in London in 2012-15, 74% HIV+
- *Clostridioides difficile*: (colon) more common in HIV+, especially in those with advanced disease (CD4 < 50)
- *Mycobacterium avium complex*: (small bowel) in those with CD4 < 50. Chronic infection with fever, sweats, weight loss, diarrhea, malabsorption, organomegaly, anemia, hepatitis

(Krones Gastrointes Clin N Am, 2012)

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Etiology: Protozoa

- *Giardia lamblia*: (small bowel) more severe, protracted disease in persons with HIV
- *E. histolytica*: (colon) more common in Asia-Pacific MSM. In Taiwan study 45% were HIV+
- *Cryptosporidia* spp (hominis and parvum): (small bowel) prolonged, severe and occasionally fatal disease. More common in underdeveloped countries but 60,000 cases annually in the US
- *Cystoisospora belli*: (small bowel): tropical and sub-tropical regions

(Krones Gastrointest Clin N Am, 2012, Wang Parasites and Vectors 2018)

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Etiology: Fungi and Viruses

- Microsporidia (*Enterocytozoon bieneusi* > *Encephalitozoon intestinalis*): (small bowel) CD4 < 100
- *Histoplasma capsulatum*: (small bowel) rare cause of diarrhea in those from endemic regions with disseminated infections

- CMV: (colon > esophagus and small bowel): CD4 < 50, causes deep painful ulcerations
- HSV: (esophagus, rectum > small bowel and colon)
- Other viruses: rotovirus, astrovirus, norovirus, sapovirus

(Krones Gastrointest Clin N Am, 2012)

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Etiology: Non-infectious

- ART associated
  - 2007(Siddiqui): PI: 38%, non-PI: 17%
  - 2013 (prescribing data) : Overall: 28%
    - PI 13.6%
    - NRTI 10%
    - NNRTI 2.2%
    - II and MRV < 1%
- Dutch study (Smit, 2013), N = 10,278

Diarrhea = reason for switching ART	Percent
1996-2000	36.2%
2001-05	24.9%
2005-2010	15.3%

(Logan, Curr Op Infect Dis 2016, Siddiqui J Clin Gastro 2007, Smit PLoS One 2013)

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Etiology: Non-infectious

- Mechanisms:
  - Enhanced Ca^{++} signaling of secretory cells → increased Cl- in the lumen followed by Na^{+} and water (Nelfinavir)
  - Increased enterocyte apoptosis → leaky epithelium (RTV and LPV - PIs)

Class/drug	Reported Incidence of diarrhea
Protease inhibitors	
Lopinavir/RTV	7-28
Atazanavir/RTV	2-3
Darunavir/RTV	9-14
Nucleoside RTI	
TDF	9-16
TAF	?
Abacavir	7
Non-nucleoside RTI	
Efavirenz	3-14
Nevirapine	< 1-2
Rilpivirine	< 2
Etravirine	0
Doravirine	3-5%
Integrase inhibitors	
Raltegravir	< 1
Dolutegravir	~ 1
Elvitegravir/C	12
Bictegravir	3-6

(Logan, Curr Op Infect Dis 2016, Clay Infect Dis Ther 2014, Dickman Dig Dis Sc 2015)

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Diagnostic Approach

- History and exam
  - Small intestine: voluminous, watery, weight loss, bloating, cramping, post-prandial diarrhea
  - Colon/rectum: tenesmus, painful defecation, hematochezia, small, frequent bowel movements
  - Organomegaly: MAC, histoplasma, cancer
- Stool examination
  - Bacterial culture, Ova and parasite exam, NA testing (biofire)
- Endoscopy
  - CMV, HSV, MAC, KS, Histoplasma

(Logan, Curr Op Infect Dis 2016, Siddiqui J Clin Gastro 2007, Smit PLoS One 2013)

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Treatment

- Targeted therapy for infectious pathogens or cancers
- Probiotics: small studies with mixed results (also cases of lactobacillus bacteremia with excessive use!)
- Diet modification: Low fat, lactose-free, high fiber, caffeine-free) why not?
- Bovine serum IgG: PC, clinical trial, N = 103 – no difference
- L-glutamine: PC study, N = 25, some benefit
- Curcumin (turmeric), single study of 8 patients: 100% effective! And who doesn't like Indian food

(Logan, Curr Op Infect Dis 2016, Siddiqui J Clin Gastro 2007, Anastasi J Assoc Nurse AIDS Care 2006)

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Treatment

- Adsobents/Anti-motility agents
  - Cochrane review: insufficient evidence for their use
  - Bismuth subsalicylate and attapulgite – unproven
  - Bulking agents (psyllium, oat bran) – do not work
  - Loperamide: (opioid receptor agonist)
    - Potential DI with PIs but does not cross the BBB so little worry
    - Familiar, established effect, safe, cheap
  - Lomotil (diphenoxylate/atropine)
    - Does cross the BBB – abuse potential
    - Those who fail loperamide generally are not rescued with Lomotil
  - Tincture of opium – abuse potential

(Logan, Curr Op Infect Dis 2016, Clay Infect Dis Ther 2014, Dickman Dig Dis Sc 2015)

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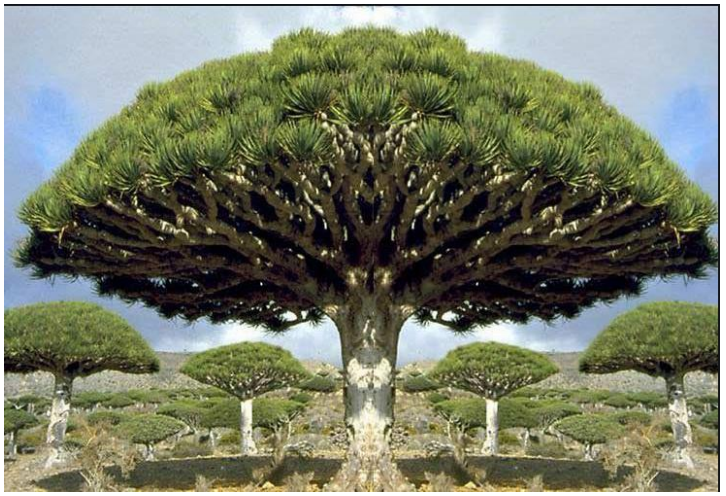
Treatment

- Anti-secretory agents
  - Octreotide: somatostatin analogue
    - Alters binding of VIP
    - Decreased diarrhea by 50% in one study of 51 patients (Cello)
    - AEs: hypo and hyperglycemia, nausea, abdominal pain
    - Is administered sub-q
    - Cost: ~$250/month

(Logan, Curr Op Infect Dis 2016, Clay Infect Dis Ther 2014, Dickman Dig Dis Sc 2015, Cello Ann Int Med 1991, MacArthur, HIV CLIN Trials 2013)

Treatment

- Anti-secretory agents
  - Crofelemer: derived from the sap of the S American tree, *Croton lechleri*
    - Inhibits Cl^- ion channels in intestinal epithelium through inhibition of Ca^{++} and cAMP activation
    - Advent study, N = 376
      - Reduced diarrhea by 17.6% (Vs 8%)
      - Not absorbed, has no DIs and no AEs
      - Cost $6-700/month (with a free on-line coupon!)



Sangre De Drago (Dragon's blood)

(Logan, Curr Op Infect Dis 2016, Clay Infect Dis Ther 2014, Dickman Dig Dis Sc 2015, Cello Ann Int Med 1991, MacArthur, HIV CLIN Trials 2013)

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Summary

- HIV-associated diarrhea remains an issue for many patients but the prevalence has decreased from nearly 100% to 28%
- Treat identified pathogens with targeted therapy
- Treat HIV enteropathy with ART
- If ART-related: Change ART: avoid PIs, Efavirenz, Cobicistat and perhaps TDF (TAF may be better)
- Non-specific therapy: loperamide, dietary changes, good Indian food
- Last resort: Octreotide or Dragon's blood

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AETC AIDS Education & Training Center Program Mountain West

National HIV/AIDS Consultation Resources

- **Clinician Consultation Center** www.nccc.ucsf.edu
- **HIV/AIDS Management (Warmline)** 1-800-933-3413
  M-F, 6am - 5pm PST
- **PEPline** 1-888-HIV-4911
  Every day, 6am - 6pm PST
- **PrEPline** 1-855-HIV-PrEP
  M-F, 8am - 3pm PST
- **Perinatal HIV Hotline** 1-888-HIV-8765
  24/7

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