

# HIV and Diarrhea in the U.S. in the post-HAART era

Amy Treakle, MD

University of Maryland Medical Center

Department of Internal Medicine

January 16, 2008





# Outline

- The basics
- GI tract review
- HIV review
  - HIV and the mucosal immune system
- Causes of Diarrhea
  - Infections (opportunistic and non-opportunistic), HIV enteropathy, GI malfunction, Medication side effects
- Resultant wasting and malnutrition
- Diagnostic algorithm

# Impact of HIV

- Global (2007)
  - 33.2million infected
  - 2.1 million deaths
- U.S. (2004)
  - 42,000 infected
  - 13,000 deaths
- Maryland (2006)
  - unknown prevalence
  - 480 deaths



# HIV and diarrhea, a history

- Prior to HAART

- 50% in developed countries
- >90% in undeveloped countries

- Since HAART

- Decline in overall mortality from 29.4 to 8.8 per 100-person years (1995-1997)
- Diarrhea still common



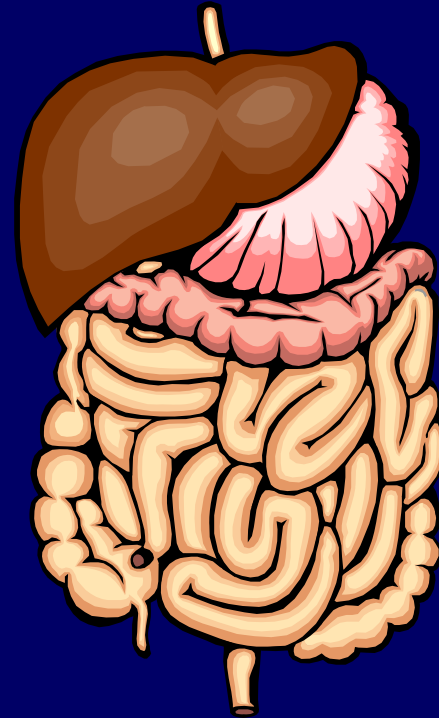
# Poo and you



- Acute v. Chronic Diarrhea
  - Chronic (CDC): two or more loose or watery stools a day for at least 30 days
- Small v. Large bowel
  - Small: large volume, infrequent, nocturnal, dehydration
  - Large: small volume, frequent, mucousy, bloody, abdominal pain, NO dehydration
- Malnutrition, electrolyte imbalance, weight loss, death

# GI tract anatomy

- Mucosa
- Submucosa
- Muscularis propria
- Adventitia



# GI tract

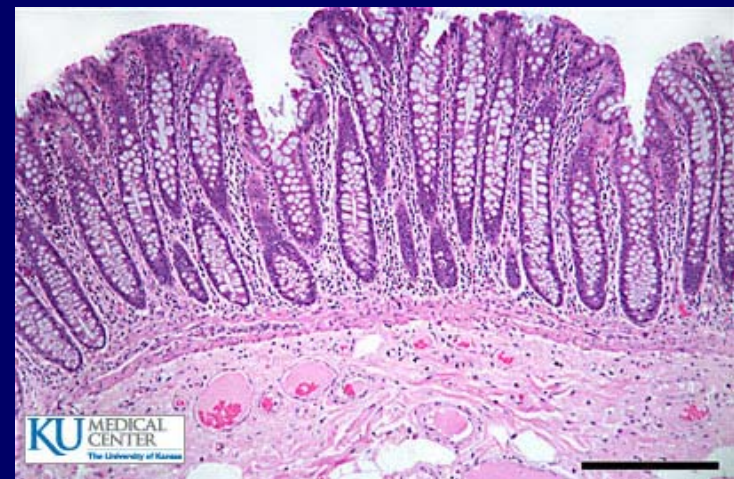
## ● Mucosa

- Squamous Cells
- Langerhaan's Cells
- Lamina propria

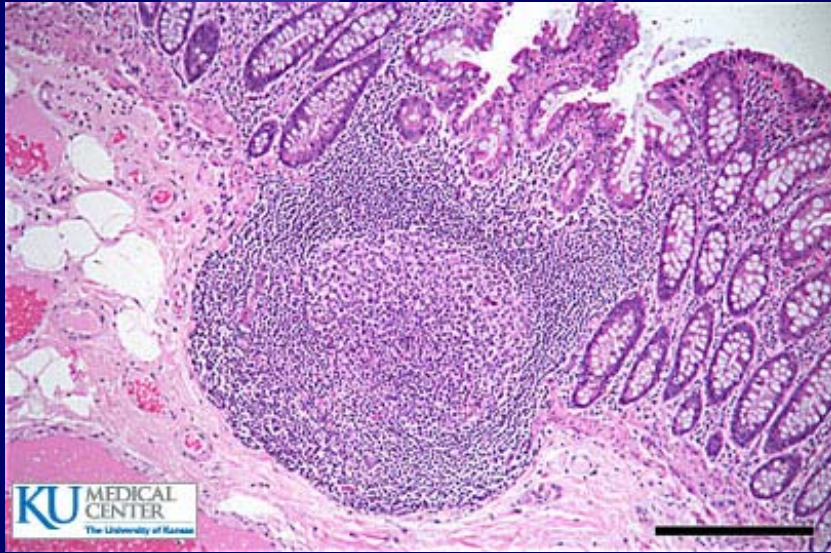
## ● Submucosa

- Lymphatics
- Nerve fibers
- Vasculature

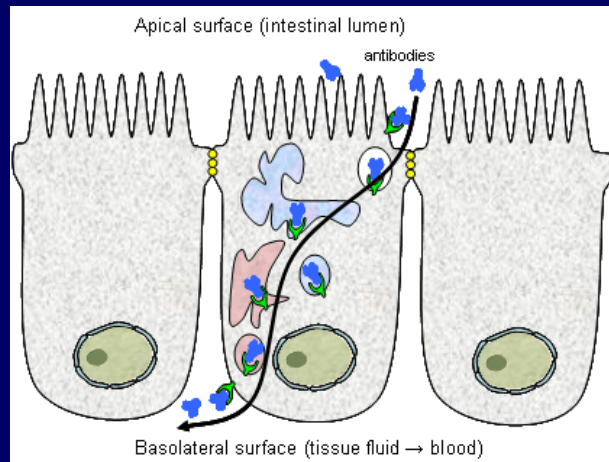
## ● Villi and crypts



# Gut Associated Lymphoid Tissue

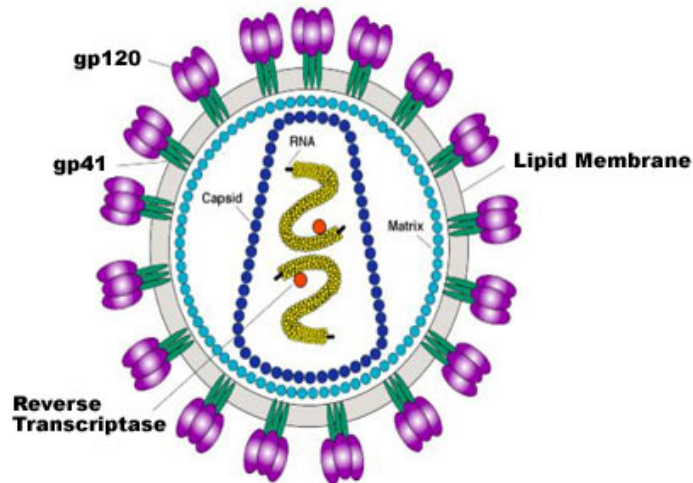


- Largest immunologic organ
- Peyer's patches and lymphoid follicles
  - Naïve B- and T-cells, Antigen Presenting Cells
  - M-Cells
    - Transcytosis
    - Potential entry sites for HIV
- Activated mucosal lymphocytes



# Human Immunodeficiency Virus

## Organization of the HIV-1 Virion



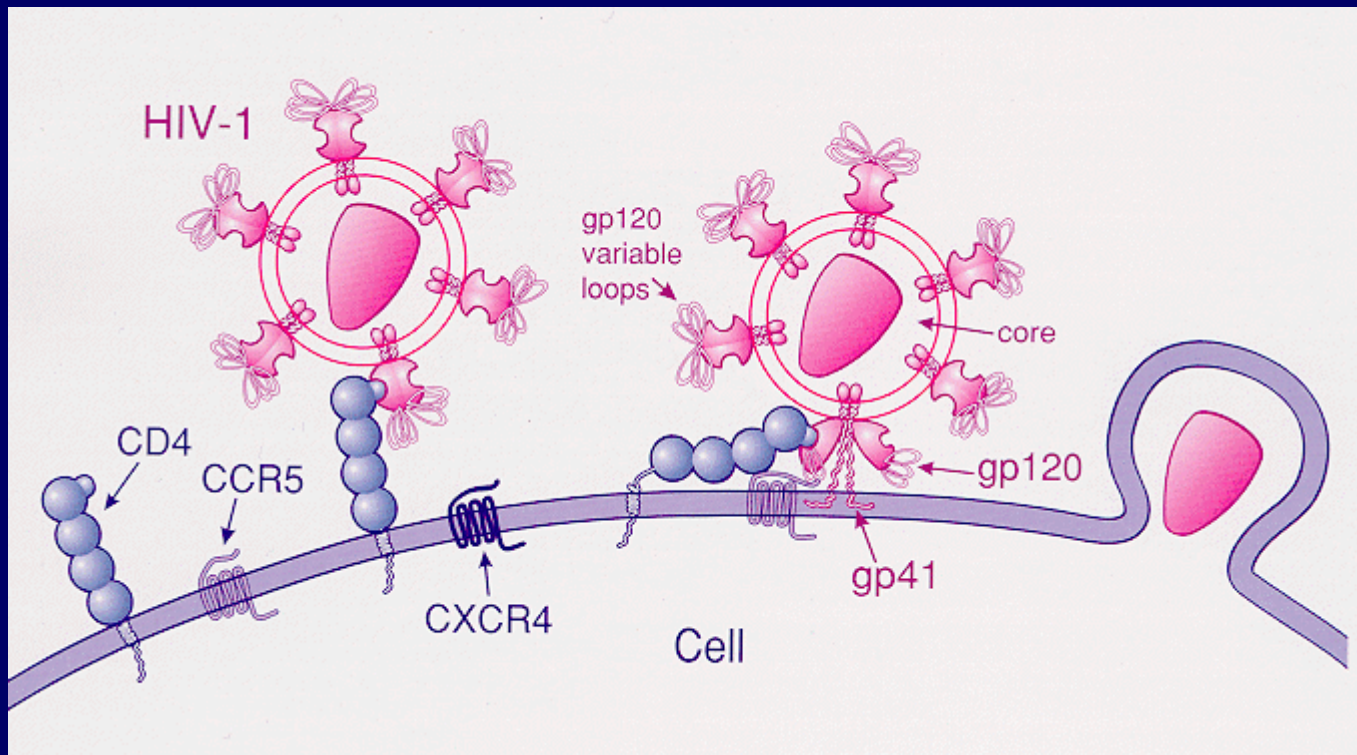
- Core

- Capsid (p24)
- RNA
- Viral enzymes
  - Integrase, Protease, Reverse Transcriptase

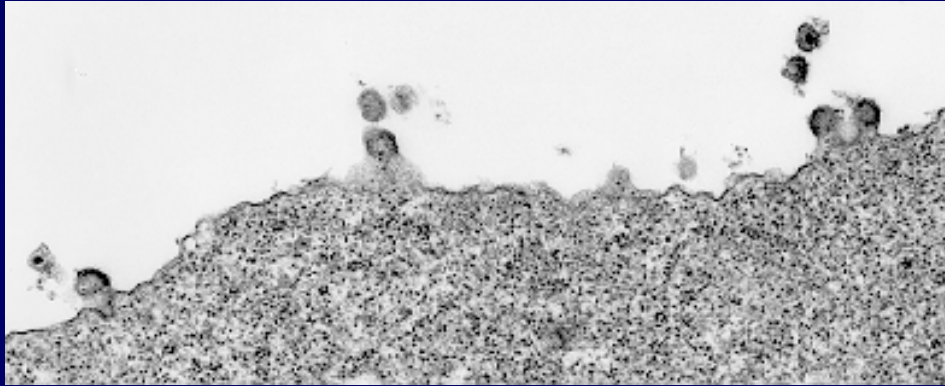
- Envelope

- gp120, gp 41

# Viral Attachment



# Cell Death



- Direct
  - Viral Budding
- Indirect
  - Apoptosis
  - gp120



# HIV and the GI tract



## ● Viral Entry

- Transcytosis
- Viral Attachment
  - Epithelial cells: GalCer (a glycolipid that attaches to gp120) and CCR5
  - Lamina propria lymphocytes: CD4, CCR5, and CXCR4

# HIV, the GI tract, and Viral Replication

- Higher in active cells
  - Higher per-cell replication than peripheral cells
  - More profound depletion than in periphery
    - Delayed restoration of GALT CD4 if HAART started late in HIV course
  - Peyer's patches relatively spared
- Viral reservoir
  - HIV present in GALT despite “undetectable” peripheral viral load

Lets stop to review...



- Diarrhea is a common symptom in HIV
- HIV
  - Multiple modes of entry
  - Kills cells via lysis or apoptosis
- GALT
  - Independent from peripheral lymph system
  - Severely depleted in HIV infection
  - Can act as reservoir for HIV



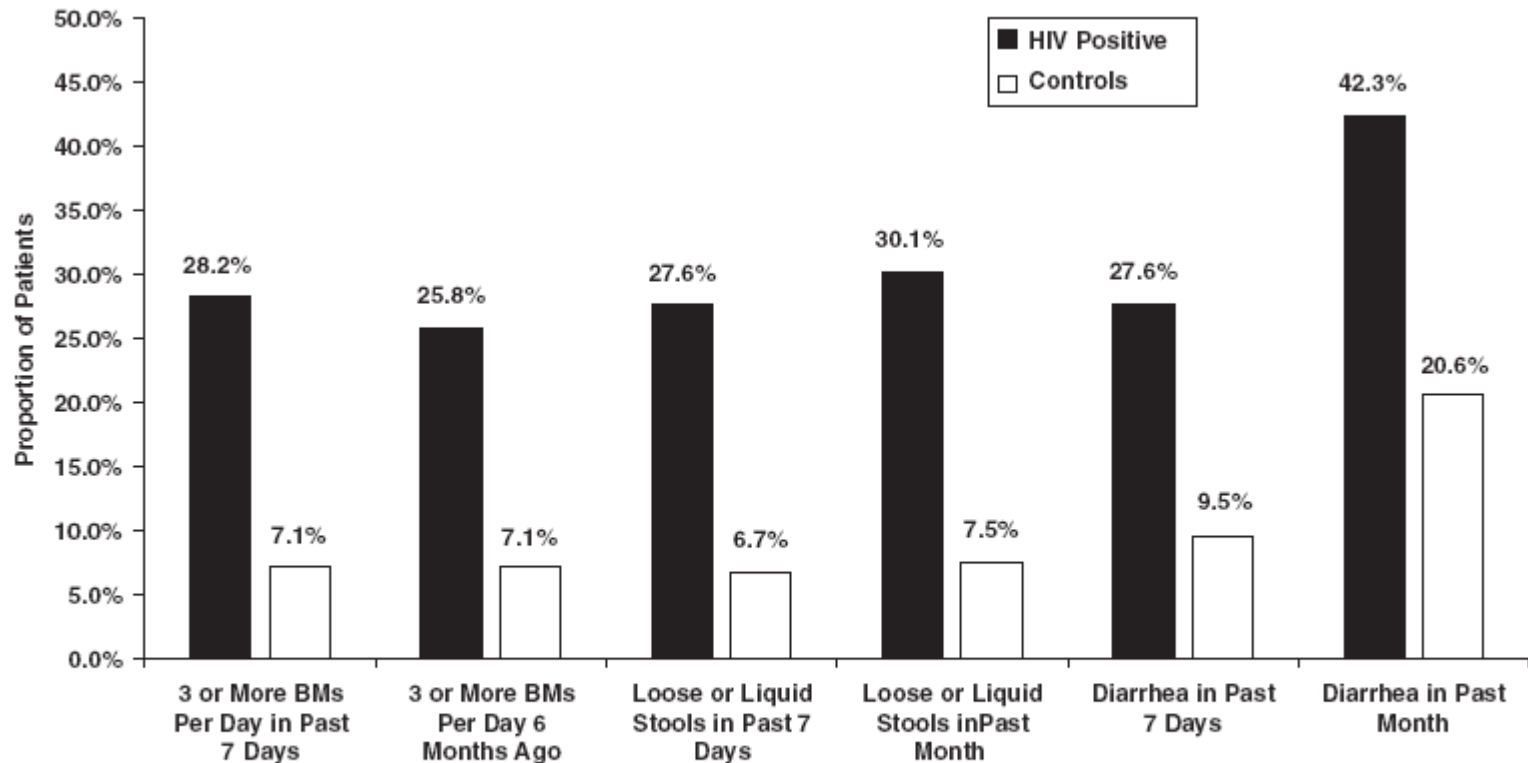
# Etiology of Diarrhea in HIV

- Opportunistic infections
- Non-opportunistic infection (Joe Schmoe Infxn)
- HIV enteropathy and GI malfunction
- Medication side effects

# Prevalence and Impact of Diarrhea

- 163 HIV+, 253 HIV- outpatients from NYC
- Survey
  - Frequency and consistency of bowel movements
  - Health related quality of life
- Mean CD4=370
  - 40 with CD4 <200
  - 150 on HAART
- Diarrhea more common in HIV (OR 6.65)
  - Even when accounting for: age, sex, race, income, education

# Prevalence and Impact of Diarrhea

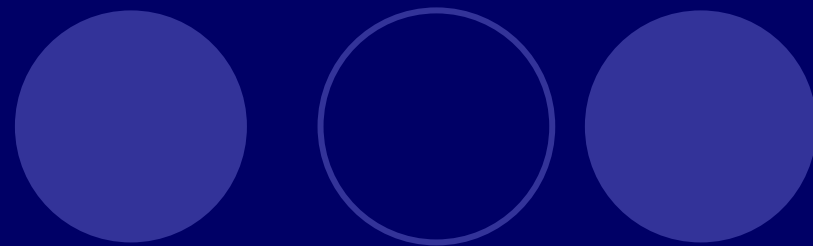
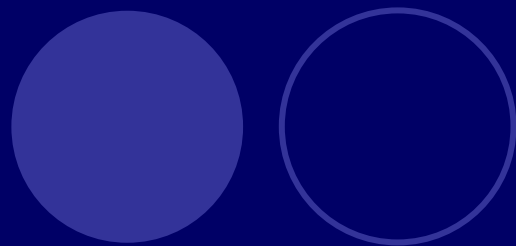


**FIGURE 1.** Proportion of patients with diarrhea among HIV-positive patients and control subjects. Diarrhea was significantly more common among HIV-positive patients than in control subjects according to several criteria ( $P < 0.001$  for all comparisons between HIV-positive patients and control subjects). BMs indicates bowel movements.

**TABLE 2.** Proportion of HIV-infected Patients With Diarrhea According to Select Demographic and Clinical Characteristics\*

	No. Subjects	Proportion With Diarrhea (%)	P
Age, years			0.002
< 40	16	18.8	
40-49	54	18.5	
50-59	67	26.9	
60 and older	26	37.7	
Sex			0.61
Female	18	33.3	
Male	145	27.6	
Race/ethnicity			0.06
White, non-Hispanic	21	47.6	
Black, non-Hispanic	102	23.5	
Hispanic or Latino	35	25.7	
Others	5	60.0	
Education $\leq$ 12 y			0.23
No	66	33.3	
Yes	97	24.7	
Annual income $\leq$ \$10,000			0.15
No	57	35.1	
Yes	106	24.5	
CD4 count, cells/mm <sup>3</sup>			0.08
< 200	40	27.5	
200-350	35	42.9	
$\geq$ 350	88	22.7	
HIV RNA undetectable			0.12
No	83	22.9	
Yes	80	33.8	
Any antiretroviral therapy			0.67
No	13	23.1	
Yes	150	28.7	
Nucleoside reverse transcription inhibitor use			0.46
No	15	20.0	
Yes	148	29.1	
Non-nucleoside reverse transcription inhibitor use			0.29
No	92	31.5	
Yes	71	23.9	
Protease inhibitor use			0.004
No	75	17.3	
Yes	88	37.5	

\*Diarrhea was defined as  $\geq$  3 bowel movements per day within the last 7 d.



**TABLE 3. Comparison of HRQOL in HIV-positive Patients and Control Subjects\***

	HIV-positive (n = 163)	Controls (n = 253)	<i>P</i>
Physical functioning	65.1 ± 30.4	83.9 ± 22.8	< 0.001
Role-physical	42.6 ± 43.5	78.5 ± 39.0	< 0.001
Bodily pain	63.7 ± 28.6	84.1 ± 23.0	< 0.001
General health	49.9 ± 23.1	74.8 ± 21.0	< 0.001
Vitality	47.6 ± 22.4	68.6 ± 25.9	< 0.001
Social functioning	60.2 ± 31.6	87.3 ± 24.1	< 0.001
Role-emotional	50.9 ± 44.8	81.6 ± 37.7	< 0.001
Mental health	62.0 ± 23.2	78.8 ± 21.1	< 0.001
Physical component summary scale	41.8 ± 10.9	50.7 ± 8.5	< 0.001
Mental component summary scale	43.5 ± 11.8	52.2 ± 11.7	< 0.001

\*HRQOL was measured using the SF-36. Scores for each of the 8 domains range from 0 to 100, with higher scores indicating better HRQOL. The physical component summary and mental component summary scales are standardized using norm-based scoring to have a mean of 50 and a standard deviation of 10 in the general US population.

**TABLE 4. Comparison of HRQOL in HIV-positive Patients With and Those Without Diarrhea\***

	Diarrhea (n = 46)	No Diarrhea (n = 117)	<i>P</i>
General health	45.3 ± 19.9	53.4 ± 22.7	0.04
Physical function	45.8 ± 22.3	73.4 ± 24.2	< 0.001
Role function	19.6 ± 35.7	49.6 ± 48.5	< 0.001
Social function	39.6 ± 22.5	56.1 ± 28.4	< 0.001
Cognitive function	81.8 ± 20.9	78.6 ± 22.2	0.39
Pain	47.1 ± 28.4	72.6 ± 27.1	< 0.001
Mental health	61.8 ± 18.0	64.9 ± 23.0	0.38
Energy/fatigue	35.2 ± 18.0	53.2 ± 21.2	< 0.001
Health distress	44.8 ± 33.6	70.9 ± 24.0	< 0.001
Quality of life	41.3 ± 24.3	65.2 ± 23.2	< 0.001
Health transition	48.4 ± 25.5	58.3 ± 23.7	0.02

\*Diarrhea was defined as ≥ 3 bowel movements per day within the last 7 d. HRQOL was measured using the MOS-HIV. Scores for each of the domains range from 0 to 100, with higher scores indicating better HRQOL.

# This study showed...

- Diarrhea more common in HIV (OR 6.65)
  - Even when accounting for: age, sex, race, income, education
- Diarrhea leads to a significant decrease in health related quality of life





# Incidence of Diarrhea

- Nutrition for Healthy Living Study
  - 671 HIV+
- Survey
  - current and chronic diarrhea
- Mean CD4 = 356, 45% on HAART
- 40% current diarrhea, 28% chronic diarrhea
  - more common in AIDS (AIDS defining illness with or without CD4 < 200)
  - not more common in just CD4 < 200

# Changing Etiology of Diarrhea

- 80 HIV+, CD4 <200 outpatients with chronic diarrhea in Birmingham, AL
- Retrospective review of etiology
  - 1995-1997, HAART (PI) introduced in 1996
- Chronic Diarrhea Incidence = 8-10.5%
- Etiology
  - Opportunistic infections, 53% to 13%,  $p=0.003$
  - Medication associated, 0 to 45%,  $p=0.001$

# Changing Etiology of Diarrhea

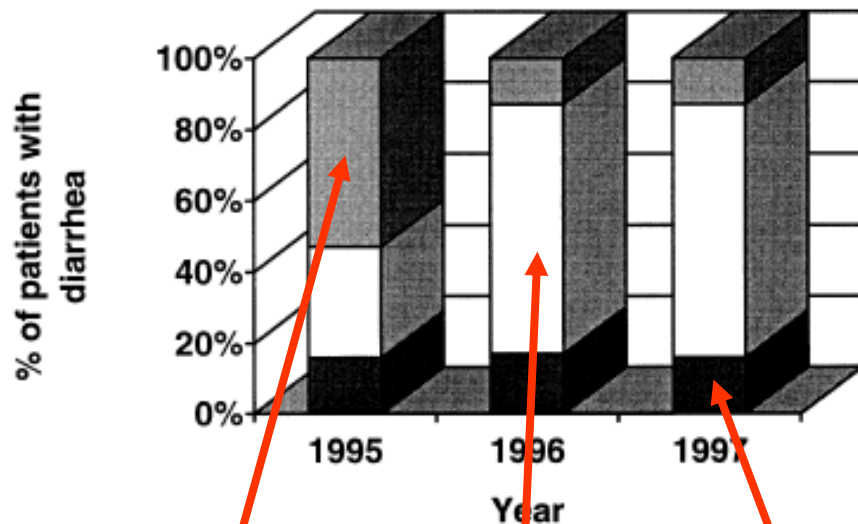


Figure 1. Etiological categories of diarrhea by year.

OI

Meds/No cause

Other  
Infxn

Table 2. Diarrhea Cases and Diagnoses by Year of Study

	Year		
	1995	1996	1997
No. patients CD4 <200	239	287	306
No. case patients (% of patients CD4 <200)	19 (8.0)	30 (10.5)	31 (10.1)
Mean CD4 cell count	43	47	80
CMV	4	3	2
Cryptosporidium	5	0	1
MAC	1	1	1
Clostridium difficile	2	4	4
Giardia lamblia	1	0	1
Salmonella	0	1	0
Medication-associated	0	4	10
No diagnosis	6	17	12

CD4 = CD4 cell count; CMV = Cytomegalovirus; MAC = *Mycobacterium avium* complex.

# Etiology of Diarrhea in HIV

- Opportunistic infections
  - Decreasing
- Non-opportunistic infection
  - Stable?
- Medication side effects
  - Increasing
- HIV enteropathy and GI malfunction
  - Becoming a new concern given longer life span



# Opportunistic Infections: Fungi



- *Histoplasma capsulatum*

- Occurs in endemic areas (Ohio, Mississippi, Missouri River valleys)
- 10% of those with disseminated infection have GI symptoms
- Amphotericin B or itraconazole

- Microsporidia

- *Enterocytozoon bienersi* and *E. intestinalis*
- Fungi v. protozoa
- Small
  - Watery diarrhea w/o fever or anorexia
- Prior to HAART
  - 20% of diarrhea if CD4<50
  - Up to 60% of chronic diarrhea
- Electron microscopy or Trichrome, Warthin-Starry and Giemsa stains
- Albendazole only effective against *E. intestinalis*

# Opportunistic Infections: Protozoa

- Small
  - Voluminous, watery diarrhea
- Chronic diarrhea
  - prolonged symptoms
  - weight loss
  - not on HAART
  - CD4 <100
- Resolution of diarrhea in 85% by raising CD4
  - Not eradication
- *Cryptosporidium spp.*
  - 10-20% of AIDS pre-HAART
  - CD4 <150
  - Reservoir: contaminated water
  - 38% have co-existing CMV
  - Nitazoxanide may treat
- *Isospora belli*
  - Less common in U.S.
  - CD4 <100
  - Bactrim, then suppression

Lewethwaite P, Gill GV, Hart CA, Beeching NJ. Gastrointestinal parasites in the immunocompromised. *Current Opinion in Infectious Diseases* 2005;18:427-35.

Oldfield EC. Evaluation of chronic diarrhea in patients with human immunodeficiency virus infection. *Rev Gastroenterol Disord* 2002;2:176-88

# Opportunistic Infections: Bacteria



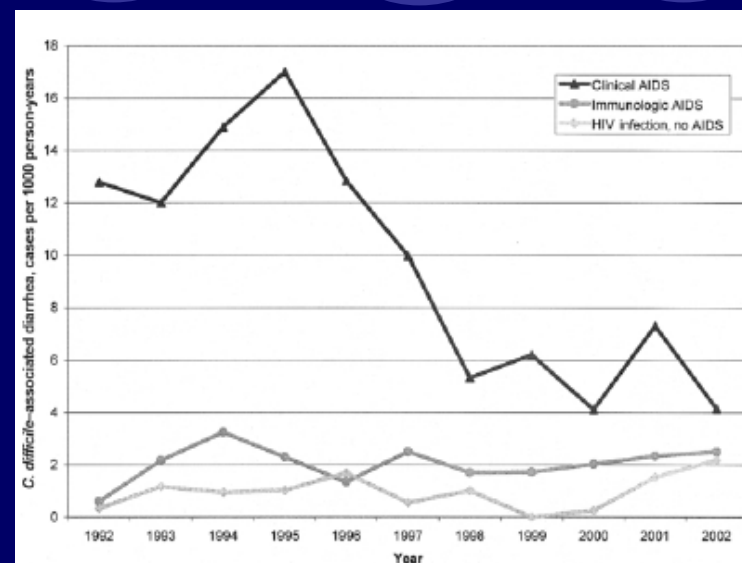
- Incidence is 7.2 per 1000 person years
  - 100-fold greater than in HIV-
- More advanced HIV = greater risk of bacterial diarrhea
- All causes decreased due to HAART

# Opportunistic Infections: Bacteria



## ● *Clostridium difficile*

- Large
- 53.6% of HIV+ with bacterial diarrhea
- Risks:
  - Prior hospital stay (p=0.04)
  - Prolonged stay (p=0.02)
  - H-2 blocker (p<0.05)
  - Tx for PCP (p<0.05)
  - Hx of herpes (p=0.03)
  - Hx of OI (p=0.04)



**Figure 1.** Trends in the annual incidence of *Clostridium difficile*-associated diarrhea (CDAD) among persons with HIV infection stratified by stage of HIV disease. Analysis includes data from 1992 through 2002 collected in >100 facilities in 9 US cities that participated in the Adult/Adolescent Spectrum of HIV Disease Project. Clinical AIDS was defined as any previous diagnosis of at least 1 AIDS-defining opportunistic infection, regardless of CD4<sup>+</sup> cell count; immunologic AIDS was defined as any previous CD4<sup>+</sup> cell count of <200 cells/mL or a CD4<sup>+</sup> cell percentage of <14% but no clinical AIDS; and HIV infection without AIDS was defined as HIV infection not defined as immunologic or clinical AIDS.

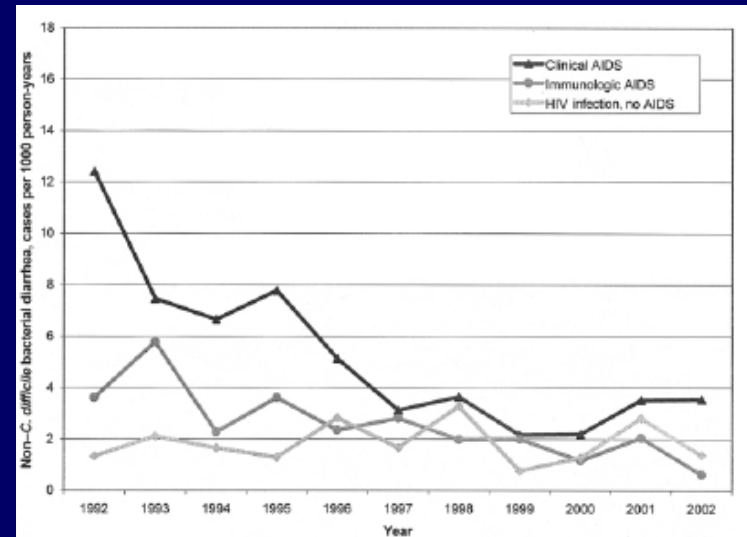
Sanchez TH, Brooks JT, Sullivan PS, Juhasz M, Mintz E, Dworkin MS, Jones JL. Bacterial diarrhea in person with HIV infection, United States, 1992-2002: Clin Infect Dis 2005;41:1621-7

Pulvirenti JJ, Mehra T, Hafiz I, DeMarais P, Marsh D, Kocka F et al. Epidemiology and outcome of *Clostridium difficile* infection and diarrhea in HIV infected inpatients. Diagnostic Microbiology and Infectious Disease 2002;44:325-30

# Opportunistic Infections: Bacteria



- *Salmonella*, *Shigella* and *Campylobacter*
  - Of HIV+ with bacterial diarrhea
    - *Shigella* = 14%
    - *Campylobacter* = 14%
    - *Salmonella* = 7.5%



**Figure 2.** Trends in the annual incidence of other bacterial diarrhea (i.e., not *Clostridium difficile*) among persons with HIV infection stratified by stage of HIV disease. Analysis includes data from 1992 through 2002 collected in >100 facilities in 9 US cities that participated in the Adult/Adolescent Spectrum of HIV Disease Project. Clinical AIDS was defined as any previous diagnosis of at least 1 AIDS-defining opportunistic infection, regardless of CD4<sup>+</sup> cell count; immunologic AIDS was defined as any previous CD4<sup>+</sup> cell count of <200 cells/mL or a CD4<sup>+</sup> cell percentage of <14% but no clinical AIDS; and HIV infection without AIDS was defined as HIV infection not defined as immunologic or clinical AIDS.

# Opportunistic Infections: Bacteria

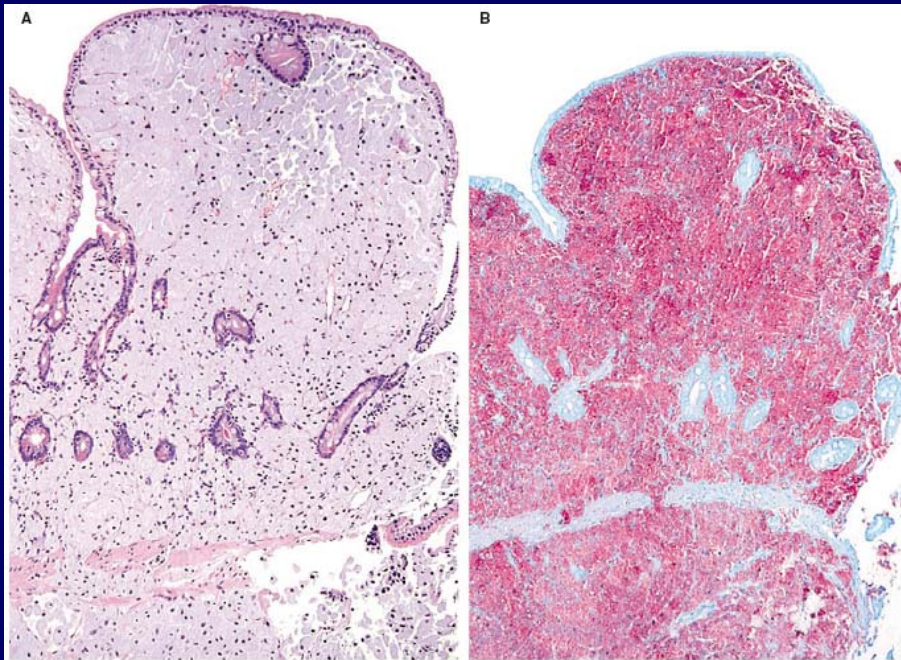


Figure 7. Low-power composite of *Mycobacterium Avium* complex in an AIDS patient. A, H&E-stained section mimicking the changes of Whipple's disease seen in Figure 5. B, AFB stain showing diffuse positivity.

- *Mycobacterium avium*-complex (MAC)
  - Small and Large
  - Prior to HAART & MAC prophylaxis, most common cause of bacterial diarrhea in AIDS
  - 2.5% in HIV+ with bacterial diarrhea
  - Diarrhea in 47% with disseminated MAC
  - CD4 <50
  - Macrolide and ethambutol +/- rifampin, long term suppression

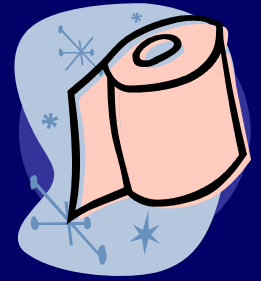
# Opportunistic Infections: Viruses

- Rotavirus, adenovirus, coronavirus, astrovirus, picobirnavirus, and calicivirus
  - More likely in HIV+ with diarrhea than without
  - Self-limiting, untreatable diarrhea
- Rectal Ulcers
- Cytomegalovirus
  - Immunocompromised
  - Colitis: chronic watery, bloody diarrhea
  - Ulceration, necrosis, perforation
  - CD 4 <100
  - 20% of diarrhea in AIDS
  - Ganciclovir or foscarnet

Grohmann GS, Glass RI, Pereira HG, Monroe SS, Hightower AW, Weber R, et al. Enteric viruses and diarrhea in HIV-infected patients. *NEJM* 1993;328:14-20.

Kartalija M, Sande MA. Diarrhea and AIDS in the era of highly active antiretroviral therapy. *Clin infect Dis* 1999; 28: 701-7

# Let's stop to review...



- Diarrhea is more common in HIV+ (OR 6.65, 10-40%)
- Diarrhea is associated with decreased health related quality of life
- Etiology of diarrhea changed due to HAART
- Notable infectious causes:
  - Fungi: *Histoplasma*, *Microsporidia*
  - Protozoa: *Cryptosporidium*
  - Bacteria: *C. difficile*, *Shigella*, *Salmonella*, *Campylobacter*, *Mycobacteria*
  - Viruses: CMV



# HIV Enteropathy and GI Malfunction

- Pathogen negative diarrhea
- Direct effects of HIV causing GI malfunction and malabsorption
- Diagnosis of exclusion



# HIV Enteropathy and GI Malfunction

- Nutrition for Health Living Study: 671 HIV+
  - Mean CD4 = 356, 45% on HAART
  - 40% current diarrhea, 28% chronic diarrhea
- GI function tests
  - CHO absorption: 25g D-xylose test
  - Fat absorption: a Sudan-III stain for fecal fat on a 100g fat diet
  - serum levels of albumin, vitamin B12, and folate

Test	Abnormal			Men	% of men	Women	% of women	<i>p</i> Value: men vs women	Non-IVDU	% of non-IVDU	% of IVDU	Value: IVDU vs non-IVDU	
	Total number	Number	% of total										
D-xylose (serum)													
<35 mg/dl	638	304	47.7	239	51.6	65	37.1	0.001	203	48.9	97	45.3	0.39
<30 mg/dl	638	193	30.3	150	32.4	43	24.6	0.055	130	31.3	60	28.0	0.40
History of liver disease	652	263	40.3	199	42.4	64	35.0	0.081	145	34.0	117	52.6	0.001
Diarrhea													
Current	653	254	38.9	196	41.6	58	31.9	0.022	176	41.2	76	34.2	0.083
Chronic	160	45	28.3	33	32.0	12	21.4	0.16	29	33.0	16	22.2	0.13
Severe	654	19	2.9	16	3.4	3	1.6	0.23	15	3.5	4	1.8	0.21
Serum vitamin B12													
<350 ng/L	632	142	22.5	112	23.9	30	18.4	0.15	106	25.5	35	16.9	0.016
<250 ng/L	632	26	4.1	18	3.8	8	4.9	0.65	22	5.3	4	1.9	0.049
Fecal fat	494	63	12.8	48	12.1	15	15.6	0.35	44	12.6	17	12.3	0.92
Stool pathogens													
Any (group 2)	499	61	12.2	59	14.7	2	2.0	0.001	54	15.5	7	4.9	0.001
Pathogenic	499	19	3.8	18	4.5	1	1.0	0.14	16	4.6	3	2.1	0.30
Albumin (<3.5 g/dl)	597	43	7.2	25	5.3	18	14.1	0.001	21	5.3	21	11.2	0.010
Serum folate (<3 µg/L)	413	3	0.7	3	0.9	0	0	1	2	0.7	1	0.8	1.00

*p* values are given from  $\chi^2$  tests.

**Table 3.** Prevalence of an Abnormality of Gastrointestinal Function Among Those With AIDS, CD4 <200, or Diarrhea

	n	AIDS	No AIDS	<i>p</i> Value	CD4 <200	CD4 >200	<i>p</i> Value	Diarrhea	No Diarrhea	<i>P</i> Value
D-xylose (<35 mg/dl)	638	50.2%	42.4%	0.061	52.6%	45.4%	0.094	50.6%	46.0%	0.26
D-xylose (<30 mg/dl)	638	34.1%	23.5%	0.006	35.8%	27.9%	0.046	32.5%	29.4%	0.41
Current diarrhea	653	41.8%	33.8%	0.044	43.2%	37.3%	0.17	NA		
Vitamin B12 (<250 ng/L)	632	4.7%	3.2%	0.39	5.9%	3.2%	0.11	2.5%	5.1%	0.11
Vitamin B12 (<350 ng/L)	632	23.6%	20.2%	0.33	30.1%	19.1%	0.003	22.2%	22.7%	0.90
Stool pathogen group 1	499	3.9%	3.8%	0.98	5.6%	3.0%	0.15	3.5%	3.9%	0.84
Stool pathogen group 2	499	10.5%	10.5%	0.86	11.3%	12.7%	0.67	9.1%	14.5%	0.073
Albumin (<3.5 g/d)	597	8.2%	8.2%	0.23	7.7%	6.8%	0.68	5.7%	8.3%	0.24

The number (n) is the total number of subjects with the gastrointestinal variable measured. Values are given as a percentage of those with or without AIDS, low CD4 count, or current diarrhea. NA = not applicable.

# This study showed...

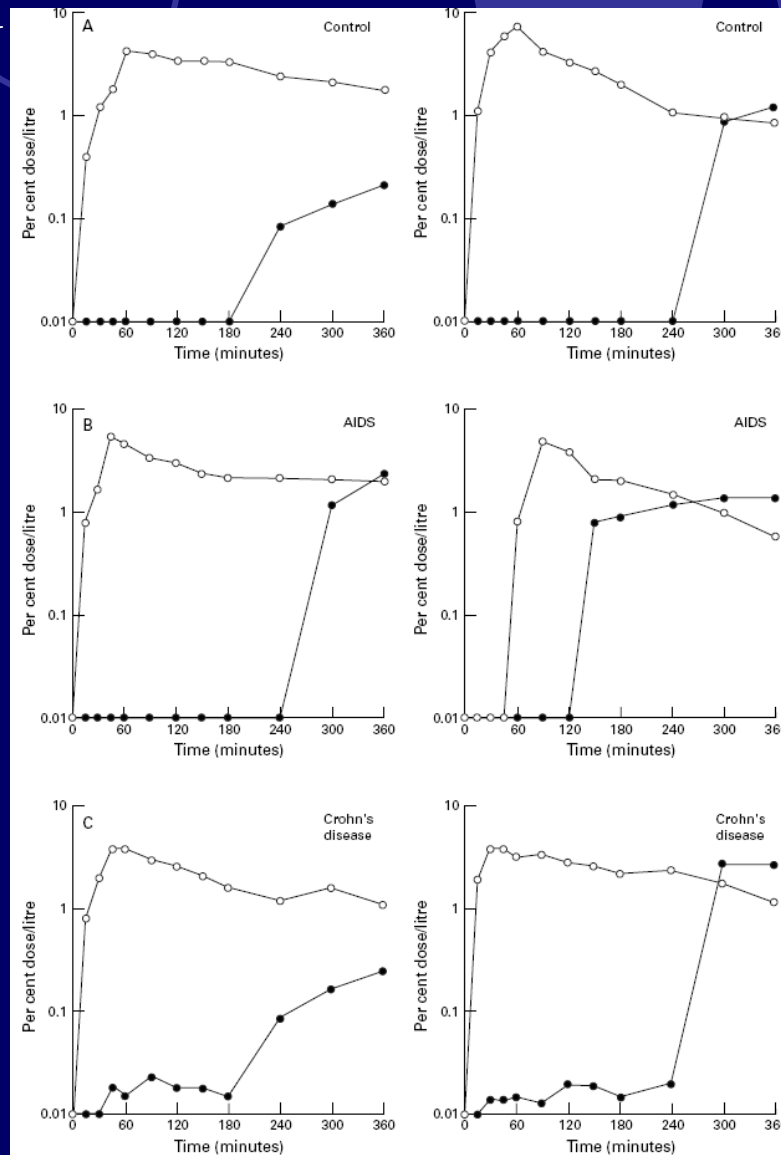


- 80% of participants had some abnormality
  - 48% had low D-xylose absorption
  - 4.1% had low serum vitamin B12
  - 13% had fat malabsorption.
- CD4 <200
  - Abnormal D-xylose absorption (p=0.046)
  - Borderline vitamin B12 absorption (p=0.003)
- fat malabsorption was just as likely regardless of CD4

# Small Intestine Transit, Absorption and Permeability

- Case-control of 60 AIDS (Stage IV), 20 HIV- controls
  - 1/3 on an antiretroviral, 94% on PCP prophylaxis
  - AIDS-well, AIDS-weight loss, Cryptosporidiosis, Microsporidiosis, CMV colitis, Pathogen negative diarrhea
- Transit
  - Orojejunal transit: glucose solution
    - Equivalent to gastric emptying time for liquid
  - Orocecal transit: sulphasalazine solution
    - Orocecal time – orojejunal time = small bowel transit
  - Crohn's controls for bacterial overgrowth
- Absorption: byproducts of 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose

# Small Intestine Transit, Absorption and Permeability



Control

AIDS

Crohn's

Figure 1 Representative permeation profiles of 3-O-methyl-D-glucose (open circles) and sulphapyridine (closed circles) after ingestion of the monosaccharide and sulphasalazine in two control subjects (A), two patients with AIDS (B), and two patients with Crohn's disease associated with small bowel bacterial overgrowth (C).

# Small Intestine Transit, Absorption and Permeability

Table 1 Gastric emptying of a liquid in AIDS

	Median time (range) in minutes of first appearance of 3-O-methyl-D-glucose in serum
Controls	15 (15-30)
AIDS, well	22.5 (15-60)*
AIDS, weight loss	30 (15-60)†
Pathogen negative diarrhoea	30 (15-45)‡
CMV colitis	30 (15-90)*
Microsporidiosis	15 (15-45)*
Cryptosporidiosis	15 (15-90)*

Statistical analysis performed by the Mann-Whitney test.

\*Differed significantly from controls ( $p < 0.05$ ).

†Differed significantly from controls ( $p < 0.005$ ).

‡Differed significantly from controls ( $p < 0.001$ ).

CMV, cytomegalovirus.

Table 2 Small intestinal absorption and permeability in AIDS

	Number	CD4 count (cells $\times 10^6/l$ )	Body mass index (weight/ height <sup>2</sup> )	3-O-m-D-glucose (% dose)	D-xylose (% dose)	L-rhamnose (% dose)	Lactulose/ L-rhamnose
Controls	20		26 (2)	47.5 (11.1)	31.7 (7.3)	12.8 (2.6)	0.03 (0.01)
AIDS, well	6	112 (146)	21 (3)*	33.4 (3.0)	23.3 (3.0)‡	5.0 (1.4)‡	0.04 (0.05)
AIDS, weight loss	11	9 (9)	18 (2)‡	31.5 (17.2)	12.5 (4.2)‡	3.4 (1.3)‡	0.14 (0.12)‡
Pathogen negative diarrhoea	10	25 (29)	19 (3)†	36.3 (14.6)	20.5 (12.1)‡	4.7 (2.3)‡	0.15 (0.09)‡
CMV colitis	12	35 (41)	20 (4)‡	39.6 (14.3)	15.5 (6.3)‡	4.2 (1.5)‡	0.20 (0.14)‡
Microsporidiosis	11	37 (52)	19 (3)‡	31.7 (16.7)	13.4 (7.1)‡	3.2 (2.1)‡	0.09 (0.06)‡
Cryptosporidiosis	10	19 (15)	18 (4)*	33.4 (12.4)	15.9 (7.0)‡	3.7 (1.7)‡	0.15 (0.14)‡

Values presented are mean (SD).

A one way ANOVA was showed significant ( $p < 0.0001$ ) differences in absorption-permeability data between the groups, apart from the 3-O-methyl-D-glucose group.

\*Differed significantly from controls ( $p < 0.05$ ; Student's *t* test using Bonferroni's correction).

†Differed significantly from controls ( $p < 0.01$ ).

‡Differed significantly from controls ( $p < 0.001$ ).

CMV, cytomegalovirus.

# Small Intestine Transit, Absorption and Permeability

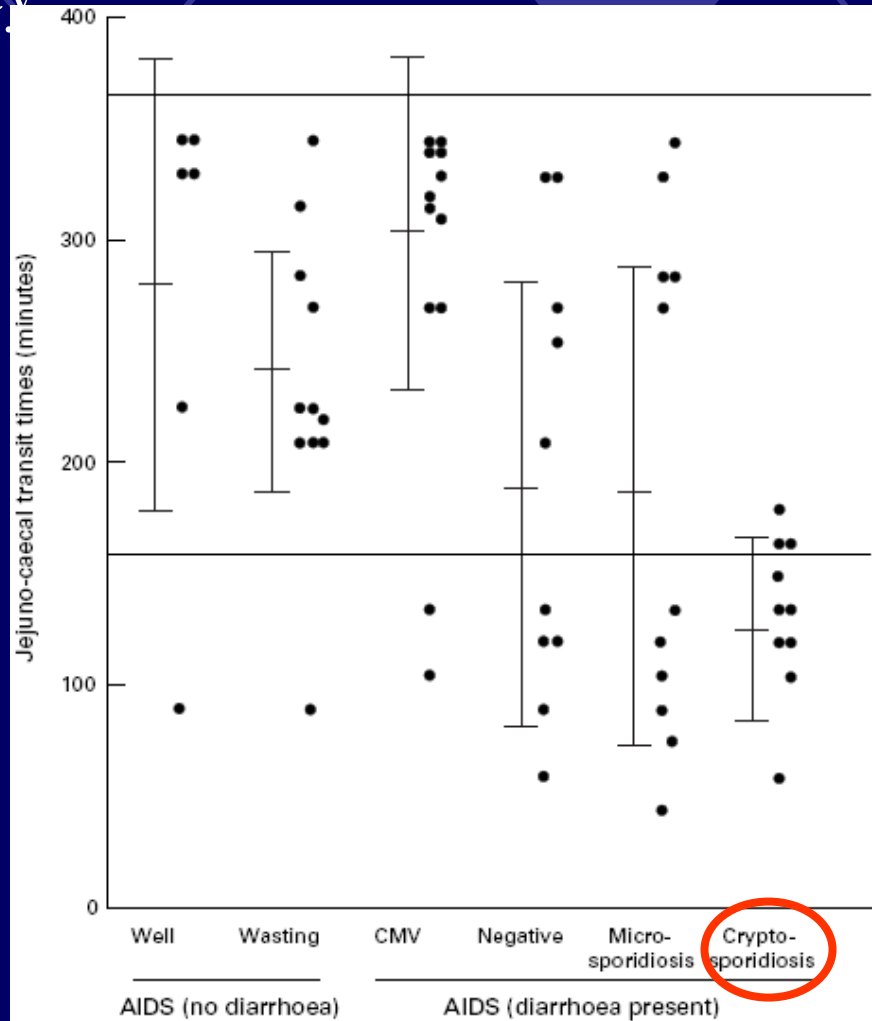


Figure 2 Individual jejunal to caecal transit times in the patients with AIDS. The two horizontal lines represent the upper and lower normal range as obtained from the 20 control subjects. Horizontal bars represent mean values and the vertical bars represent SD.

# This study showed...

- GI malfunction

- Carbohydrate malabsorption
- Trend toward decreased small bowel transit time
- Delayed gastric emptying time
- Bacterial overgrowth is not likely



# HIV Enteropathy and GI Malfunction

## ● Fat absorption

- HIV+ with chronic diarrhea, 24-hour stool specimen for fecal fat
- 95% off HAART, 83% on HAART
- No difference with or without stool pathogen

## ● Neuropathy

- Extensive damage to autonomic nerve fibers in the lamina propria

Poles MA, Fuerst M, McGowan I, Elliott J, Rezaei A, Mark D, et al. HIV-related diarrhea is multifactorial and fat malabsorption is commonly present, independent of HAART. *Am J Gastroenterol* 2001; 96: 1831-7.

Griffin GE, Miller A, Batman P, Forster SM, Pinching AJ, Harris JR, et al. Damage to jejunal intrinsic autonomic nerves in HIV infection. *AIDS* 1988;2:379-85

# HIV Enteropathy and GI Malfunction

- Jejunul mucosal changes
  - decreased surface area to volume ratio
  - shortened villi
  - normal crypt length with increased mitoses
  - leading to an overall atrophy with epithelial hypoproliferation and dysmaturation of enterocytes

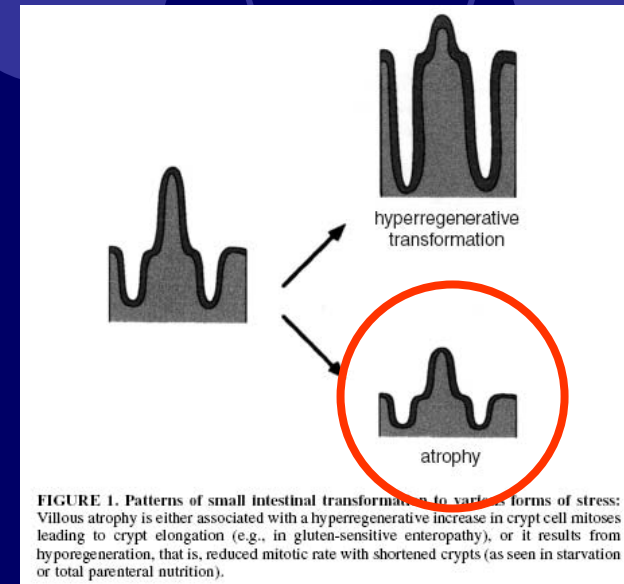


TABLE 1. HIV/SIV enteropathy<sup>a</sup>

	Late Phase of Infection (Humans)	Early Phase of Infection (Nonhuman Primates)
CD4+ T cells	↓↓	↓↓
CD8+ T cells	↑↑	↑↑
Activation of CD8+ T cells	(↑)	↑↑
Villous height	↓	↓
Crypt depth	↔	↔
Crypt cell proliferation	(↓)	↑
Brush-border enzyme activity	↓↓	?

<sup>a</sup>Summary of the main findings in HIV infection in humans and in the early phase of SIV infection in nonhuman primates (up to 12 weeks): The relative proportions of lamina propria T cells were investigated by flow cytometry of isolated cells. Mucosal architecture was studied by microdissection and morphometry.

Zeit M, Ullrich, R, Schneider T, Kewenig S, Hohloch K, Riecken EO. HIV/SIV enteropathy. *Annals of the New York Acad Sci* 1998; 859: 231-6

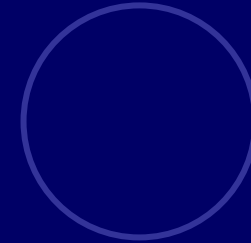
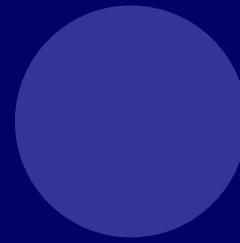
Batman PA, Kapembwa MS, Miller ARO, Sedgwick PM, Lucas S, Sewankambo NK, et al. HIV enteropathy: comparative morphometry of the jejunal mucosa of HIV infected patients resident in the United Kingdom and Uganda. *Gut* 1998; 43:350-355.

Cummins AG, LaBrooy JT, Stanley DP, Rowland R, Shearman DJC. Quantitative histological study of enteropathy associated with HIV infection. *Gut* 1990; 21:317-21.

# HIV Enteropathy and GI Malfunction

- Possible direct effects by HIV
  - increased intercellular permeability by decreased electrical resistance
  - cytoskeletal changes (tubulin depolymerization)
  - changes in cytosolic calcium by incubation of gp120 with intestinal cells
    - associated with cytoskeletal depolymerization and decreased epithelial resistance

Lets stop to review...



- GI malfunction

- Carbohydrate malabsorption
- Fat malabsorption
- Trend toward decreased small bowel transit time
- Delayed gastric emptying time

- Neuropathy

- Jejunal villous atrophy

- Intracellular mechanism

# Medication Side Effects

<u>Class</u>	<u>Generic Name</u>	<u>Brand Name</u>	<u>Incidence</u>
Protease Inhibitors	Ritonavir	Norvir	19-37%
	Ritonavir/ Loprinavir	Kaletra	24-26%
	Nelfinavir	Viracept	32%
Nucleoside Analogues	Abacavir	Ziagen	17%
	Didanosine*	Videx	5-18%



# Malnutrition

- Caused by:
  - Difficulty eating (esophagitis, altered taste perception, dysphagia)
  - Malabsorption
  - Diarrhea
  - Increased energy expenditure due to infection
- Increased mortality
  - Weight loss of 10% from baseline had a 6-fold increase in mortality, including those on HAART ( $p < 0.05$ )

Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J Acq Immune Defic Syndr* 2002;31: 230-6

## Complete History and Physical Examination

Exclude dietary causes and discontinue potential diarrheal causing medications if possible.

Evaluate travel history and sexual practices.

Assess CD4 cell count and maximize therapy for all diagnosed pathogens.

Determine severity and characteristics of diarrhea: acute vs chronic (>4 wks), fevers, inflammatory (hematochezia).

Evaluate orthostatic changes, nutritional status, abdominal examination with focal findings, rectal examination etc.

Diarrhea suggestive of small bowel disease includes the presence of crampy abdominal pain, large volume, infrequent, nocturnal diarrhea, malabsorption. Large bowel disease includes frequent, small volume, mucous, bloody diarrhea.

## Stool Studies

Stool cultures  $\times$  2-3; if patient has fevers also obtain blood cultures (evaluate for salmonella, shigella, campylobacter, and *Escherichia coli*).

Direct or concentrated stool specimens for ova and parasites  $\times$  3: saline and iodine preparations (giardia, entamoeba, isospora).

Acid-fast stain of stool and parasitic examination (cryptosporidia, cyclospora, isospora, MAC).

Assay for *Clostridium difficile* toxin (especially if patient has had recent antibiotic use or hospitalization).

Modified trichrome stains\* (microsporidia).

Immunofluorescence or ELISA (cryptosporidia, giardia, isospora).

Stool culture for *Mycobacterium*†.

Stool viral studies\* including electron microscopy or viral antigen detection by ELISA (adenovirus, astrovirus, rotavirus).

### Stool or blood cultures positive

salmonella  
shigella  
campylobacter  
mycobacterium

### Negative stool studies

### *C. difficile* toxin assay positive

### Microscopic exam positive

O&P: Giardia, Entamoeba

Acid-fast stain: MAC, isospora, cryptosporidia, cyclospora

Modified trichrome stain:  
microsporidia

ELISA, immunofluorescence stain  
cryptosporidia, isospora,  
giardia, cyclospora

Endoscopic examination (for persistent diarrhea after multiple negative stool studies) to obtain biopsy specimens. Search for any ulcers, pseudomembranes, and other lesions. If ulcers are present, biopsy the ulcer margin.

If the clinical evaluation is suggestive of small bowel disease or malabsorption (an abnormal D-xylose testing), proceed with upper endoscopy with distal small bowel biopsy and aspirates. If symptoms suggestive of colonic disease, proceed with colonoscopy or flexible sigmoidoscopy with colon and even terminal ileal biopsies if possible. If unable to clinically distinguish between small or large bowel disease, both procedures may be necessary for diagnosis and can be performed on the same visit.

### Upper endoscopy with small bowel biopsies

Histologic examination including:

H & E (especially for protozoa and viral inclusion cells):

cryptosporidia, Isospora, CMV, microsporidia)

Acid-fast stain\* (for cryptosporidia, isospora, MAC)

Ciema staining (giardia, microsporidia)

Methenamine silver staining (histoplasmosis).

Duodenal aspirate for culture, O & P.

Electron microscopy\* (microsporidia).

In situ hybridization and immunohistochemistry\* (CMV).

Viral culture (CMV) and mycobacterial culture†.

### Colonoscopy or flexible sigmoidoscopy with colon biopsies

Histologic examination including:

H & E (especially for protozoa, viral inclusion cells, and bacteria):

cryptosporidia, Entamoeba, CMV, HSV, E. Coli)

Acid-fast stain\* (cryptosporidia, MAC)

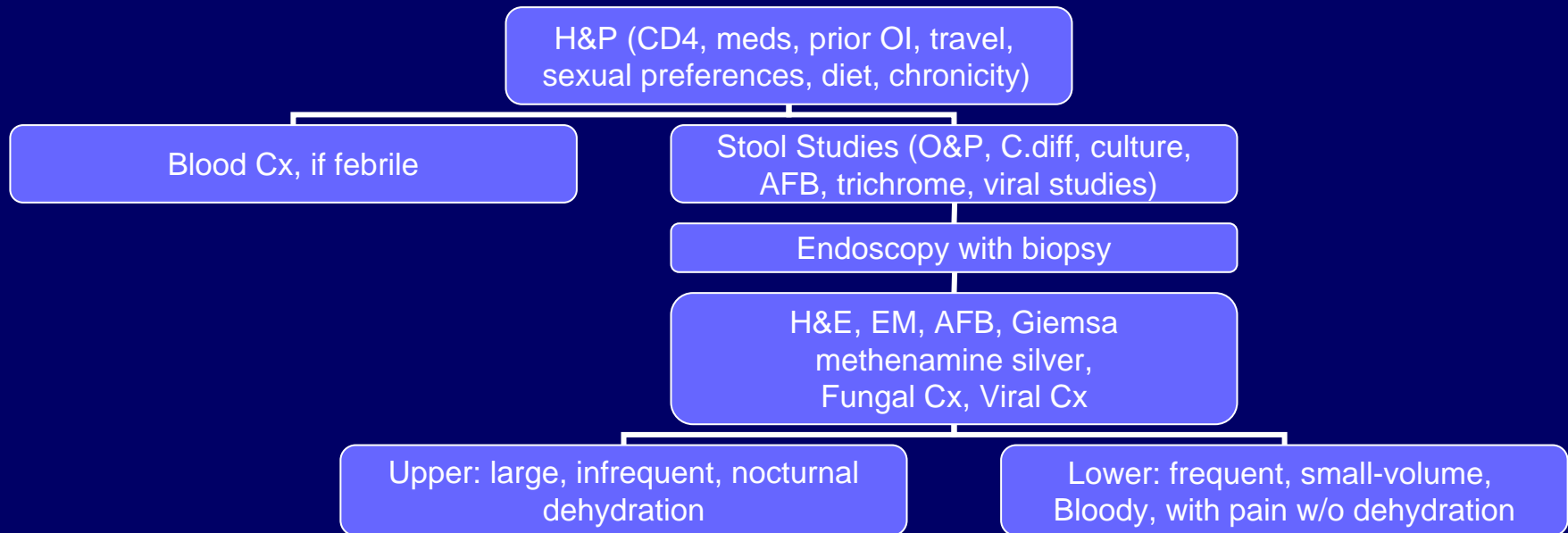
Methenamine silver staining (histoplasmosis).

Electron microscopy\* (adenovirus).

Fungal culture\* (histoplasmosis).

Viral culture (CMV, HSV, adenovirus) and mycobacterial culture†.

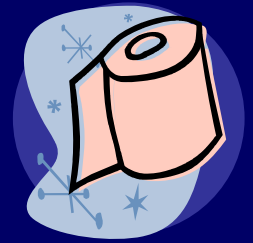
# Diagnostic Algorithm



# Conclusions

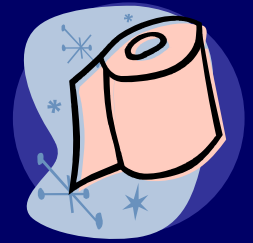


# Conclusions



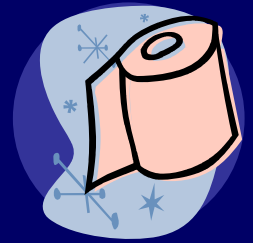
- GI mucosal immune system
  - is independent from peripheral immune system
  - is a potential site of entry for HIV
  - is a potential reservoir for HIV
  - is depleted in HIV
    - can recover fully if HAART is started early in course

# Conclusions



- Diarrhea is more prevalent in HIV+
- Infectious Causes
  - Declining due to HAART
  - Fungi: *Histoplasma*, *Microsporidia*
  - Protozoa: *Cryptosporidium*
  - Bacteria: *C. difficile*, *Shigella*, *Salmonella*, *Campylobacter*, *Mycobacteria*
  - Viruses: CMV

# Conclusions



- HIV Enteropathy/GI Malfunction
  - Possibly due to direct effects from HIV
  - Decreased fat and carbohydrate absorption
  - Trend toward decreased small bowel transit time
  - Jejunal atrophy
  - Neuropathy
  - Not likely due to: bacterial overgrowth
- Medications (PIs and NRTIs) have high incidence of diarrhea



The End!

Any questions?

Many thanks to Lori Fantry, MD MPH