An Approach to Chronic Diarrhoea

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Declarations

OUTLINE

- Introduction
- HIV and the GIT
- Pathogens
- Diagnostic algorithm
- Treatment
- Conclusion

Chronic Diarrhoea in HIV

- With expanded roll-out of ART
  - Decreased mortality associated with HIV
  - Life expectancy has increased even in LMIC
- Over half of people living with HIV (PLHIV) experience diarrhoea
  - Negatively contributes to quality of life & adherence to ART
  - Common cause to switch or discontinue ART
- With global use of ART
  - Incidence of diarrhoea due to opportunistic infections has decreased
  - Incidence of noninfectious diarrhoea has increased
- The differential diagnosis for diarrhoea in PLHIV is broad

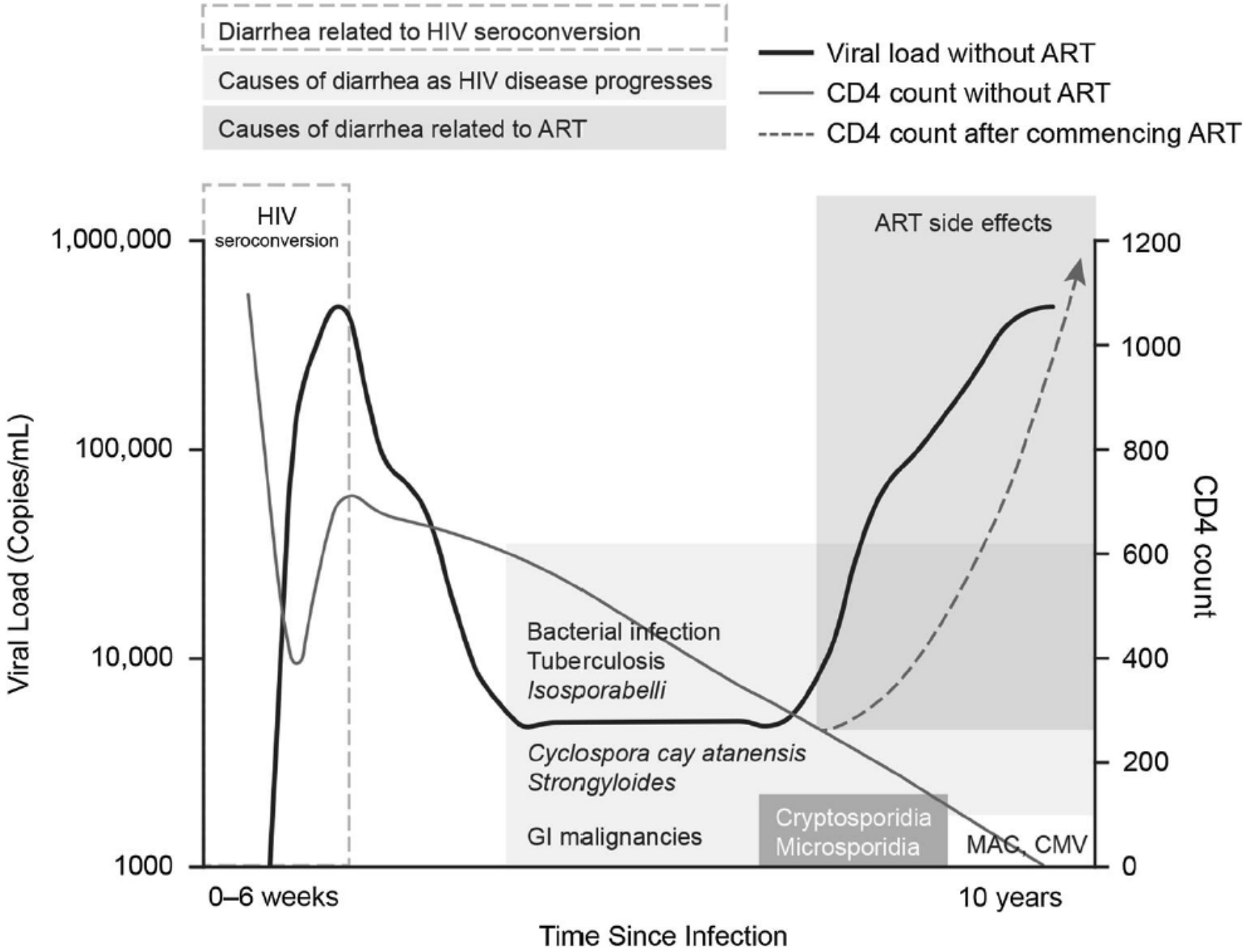
Chronic Diarrhoea in HIV

- Working definition of diarrhoea;
  - Abnormal passage of ≥ 3 unformed stools per day or a liquid stool volume >200 g/d
  - chronic: diarrhoea of duration >4 weeks
  - Severe diarrhea: ≥10 viscous, liquid, or watery stools in a 24 hour period
- Establishing a cause will include:
  - History- patient's HIV & treatment history, potential pathogen exposure (travel history)
  - Physical examination
  - Laboratory investigations

HIV and the GIT

- Gut- associated lymphoid tissue (GALT)- largest collection of lymphoid tissue
- GI tract targeted during all phases of HIV infection
  - Effects of HIV on the mucosal immune system most apparent in acute infection
  - Within weeks of infection, vast majority of mucosal lamina propria CD4+ lymphocytes are depleted
- In chronic HIV infection
  - mucosal environment contains- paucity of CD4+ T cells
  - but overpopulated with CD8+ T cells & B cells
  - giving wrong impression of a healthy mucosal environment at microscopic level

Dig Dis Sci 2015; 60:2236-2245



Dig Dis Sci. 2015;60:2236-2245

Pathogens

- Multitude differences in the standard of living in LIMC & HIC
  - Incidence & type diarrhoea-associated infections may vary by region
- Opportunistic infections can be categorized into 4 groups
  - Bacteria
  - Fungi
  - Viruses
  - Protozoa
- Idiopathic diarrhoea

Pathogen	Endoscopy	Colonoscopy
Bacteria	*Salmonella*	*Salmonella, Shigella, Campylobacter*
	Enteropathogenic and enterotoxigenic *Escherichia coli* (small intestine)	Enterohemorrhagic *E coli,* enteroinvasive *E coli*
	Small intestine bacterial overgrowth	*Clostridium difficile*
	Mycobacterium avium complex	*Mycobacterium avium* complex
Protozoa	*Cryptosporidia* (small intestine)	*Cryptosporidia*
	Microsporidia (most often in proximal jejunum)	*Entamoeba histolytica*
	Giardia (upper small intestine)	
	Cyclospora (small intestine)	
	Isospora (small intestine)	
Viruses	CMV	CMV
	HSV	HSV (rectum, sigmoid)
		Adenovirus
Fungi	*Histoplasma* (most commonly terminal ileum; can affect any part of the GI tract)	*Histoplasma* (most commonly terminal ileum; can affect any part of the GI tract)

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ART class	Reported incidence of diarrhea (%)
Protease inhibitors	
Lopinavir/ritonavir	7–28
Atazanavir/ritonavir	2–3
Darunavir/ritonavir	9–14
Nonnucleoside reverse transcriptase inhibitors	
Efavirenz	3–14
Nevirapine	<1–2
Rilpivirine	<2
Nucleoside reverse transcriptase inhibitors	
Tenofovir disoproxil fumarate	9–16
Abacavir	7
Integrase inhibitors	
Raltegravir	<1
Dolutegravir	~1
Elvitegravir[a]	12

Dig Dis Sci. 2015; 60:2236-2245

- ART / HAART-associated diarrhoea caused by a variety of mechanism
  - Increased calcium-dependent chloride conductance & cellular apoptosis
  - Induce endoplasmic reticulum (ER) stress & activation of intestinal epithelial cells
- Autonomic Neuropathy
  - Structural damage & depletion of autonomic nerves- occur all stages of HIV infection
- Chronic pancreatitis & Exocrine insufficiency
- Kaposi’s sarcoma
- Non-Hodgkin’s lymphoma

Idiopathic diarrhoea

Condition	Clinical Presentation/Definition
HIV enteropathy [36]	May be associated with GI inflammation Malabsorption of vitamin B12 and bile acid Increased intestinal permeability Weight loss Histologically associated with Inflammatory lymphocyte infiltrates Damage to the GI epithelium, including villous atrophy, crypt hyperplasia, and villous blunting

Condition	Clinical Presentation/Definition
Irritable bowel syndrome [37]	Defined by the ACG as abdominal pain or discomfort associated with altered bowel habits over a period of ≥3 months Defined by Rome III criteria as recurrent abdominal pain or discomfort for ≥3 d/mo in the last 3 months with symptom onset at ≥6 months before diagnosis and associated with ≥2 of the following: Improvement with defecation Onset associated with change in stool frequency Onset associated with change in stool form

Condition	Clinical Presentation/Definition
Functional diarrhea [37]	Defined by Rome III criteria as ≥75% of stools that are loose (mushy) and without pain for ≥3 months with symptom onset ≥6 months before diagnosis

Clin infect Dis. 2012; 55:860-867

Impact of antiretroviral drugs on the microbiome: unknown answers to important questions

Sandra Pinto-Cardoso[a], Nichole R. Klatt[b], and Gustavo Reyes-Terán[a]

- ART does not completely reverse damage to gut mucosa epithelia
- ARV drug combinations have differential effects on:
  - the gut microbiome
  - markers of microbial translocation, inflammation / immune activation
  - gut epithelial barrier damage
- Despite effective ART key commensal species including butyrate-producing bacteria remain depleted

Curr Opin HIV AIDS. 2018;13:53-60.

Unusual Causes of Diarrhoea

Strongyloides Stercoralis Infection Among Human Immunodeficiency Virus (HIV)-Infected Patients in the United States of America: A Case Report and Review of Literature

- Tropical & subtropical regions most affected by S. stercoralis (prevalence of 85% in low socioeconomic populations)
- S. stercoralis disseminated disease & hyper-infection syndrome rare in HIV-infected individuals
- Two main risk factors for developing life-threatening hyper-infection syndrome (in HIV)
  - Use of steroids & co-infection by human T-lymphotrophic virus type 1 (HLTV-1)
- In non-endemic areas route of transmission made be by person-to-person sexual contact

Am J Case Rep. 2017; 18: 339-346.

OPEN ACCESS Freely available online

PLoS one

Failure to Eradicate *Isospora belli* Diarrhoea Despite Immune Reconstitution in Adults with HIV - A Case Series

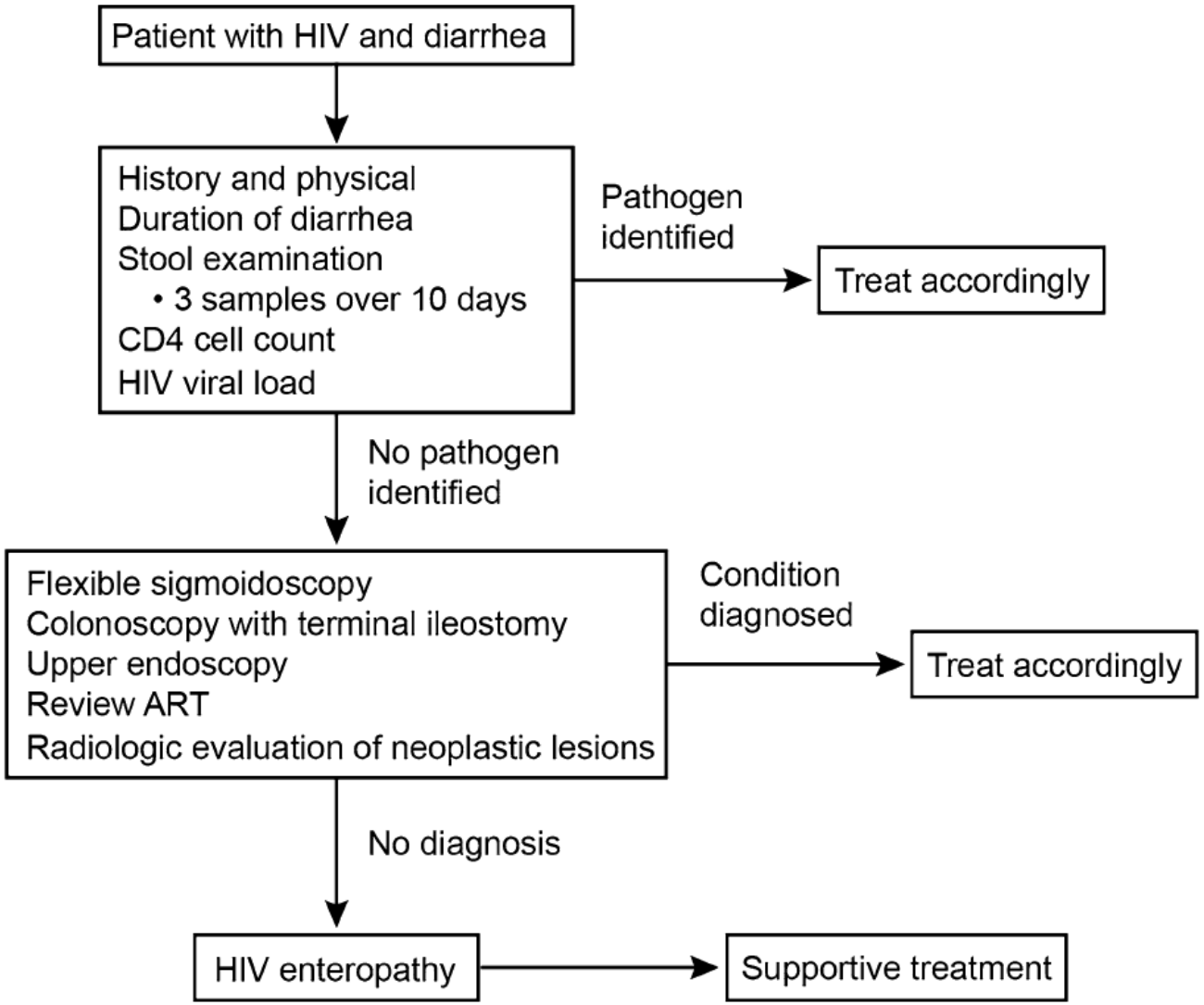
Tom H. Boyles[1*], John Black[1], Graeme Meintjes[1,2,3], Marc Mendelson[1]

Abstract

Isospora belli causes diarrhoea in patients with AIDS. Most respond to targeted therapy and recommendations are that secondary prophylaxis can be stopped following immune reconstitution with ART. We report eight cases of chronic isosporiasis that persisted despite standard antimicrobial therapy, secondary prophylaxis, and good immunological and virological response to ART. Median CD4 nadir was 175.5 cells/mm^3 and median highest CD4 while symptomatic was 373 cells/mm^3. Overall 34% of stool samples and 63% of duodenal biopsy specimens were positive for oocytes. Four patients died, two remain symptomatic and two recovered. Possible explanations for persistence of symptoms include host factors such as antigen specific immune deficiency or generalised reduction in gut immunity. Parasite factors may include accumulating resistance to co-trimoxazole. Research is required to determine the optimum dose and duration of co-trimoxazole therapy and whether dual therapy may be necessary. Mortality was high and pending more data we recommend extended treatment with high-dose co-trimoxazole in similar cases.

PLoS ONE 2012; 7(8):e42844

Diagnosis



Clin infect Dis. 2012; 55:860-867

Class	Mechanism of action	Examples
Adsorbents	Adsorb fluids to improve stool consistency	Attapulgite Bismuth subsalicylate Kaolin[a] Pectin
Antimotility agents	Increases fecal transit time by decreasing bowel activity, thereby reducing fluid and electrolyte loss	Diphenoxylate–atropine Loperamide Octreotide
Antisecretory agents	Inhibits secretion of water and electrolytes into the GI tract	Crofelemer Octreotide Racecadotril

Dig Dis Sci. 2015; 60:2236-2245

Conclusion

- Over half of patients with HIV experience diarrhoea
- The incidence of diarrhoea because of opportunistic infections has decreased
- The incidence of noninfectious diarrhoea has increased
- Pharmacologic options for noninfectious diarrhoea limited
- Addressing diarrhoea in HIV-infected individuals remains important

THANK YOU!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