Advanced HIV Disease

Approach to Diarrhoea in people with HIV

Dr. D Stead
Infectious diseases specialist physician
Frere Hospital, East London
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WSU Walter Sisulu University

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Advanced HIV Disease (AHD)

- WHO definition (adults & adolescents):
  - CD4 <200 cells/mm^3 and/or
  - WHO clinical stage 3 or 4
- Despite ‘test and treat’ policy, up to half of all people living with HIV present to care with AHD
- Either ARV naïve, or interrupted therapy, or on failing regimen
- AHD has a higher mortality risk

Diarrhoea in people living with HIV (PLWH)

- Affects 40-80% not on ART
- 25% of deaths in a rural SA ART program from gastroenteritis[1]
- Limited access to water associated with increased diarrhoea in HIV[2]

- Definition of diarrhoea:
  - ≥ 3 loose/ liquid stools per 24 hours

(1. Macpherson P, et al. Mortality and loss to follow-up among HAART initiators in rural South Africa. Trans R Soc Trop Med Hyg. 2009
2. Moshabela, M et al. Clinical and social determinants of diarrhoeal disease in a rural HIV/AIDS clinic, South Africa: a case-control study Int J STD AIDS. 2012 May)

Aetiologies of diarrhoea in HIV: Infectious

- Bacterial
  - *Salmonella typhi*
  - *Shigella*
  - *Campylobacter*
  - *Entero-invasive E. coli*
  - *Clostridium difficle*
  - *Mycobacterial (MTB, MAC)**
- Viral
  - *CMV**
  - *HIV (HIV enteropathy)**
  - *Others (Adeno-, entero- etc.)*

* HIV associated

- Protozoal
  - *Cryptosporidium**
  - *Cystoisospora belli (Isospora b.)**
  - *Microsporidium**
  - *Entamoeba histolytica*
  - *Giardia*

Reported stool pathogen prevalence in SA

	GF Jooste hospital (n=209)[1]	Vhembe, Venda (n=269)[2]
Cryptosporidium	29%	25%
Cystoisospora belli	21%	6%
Shigella	14%	NS
Salmonella	5%	NS
Giardia	5%	15%
Campylobacter	4%	NS
Entamoeba histolytica	NS	34%
Cyclospora	NS	12%

(1. unpublished personal correspondence
2. Samie A, et al. *J Heal Popul Nutr*. 2009)

Protozoal diarrhoeal disease in AHD

- *Cryptosporidium, cystoisospora belli, microsporidium*
  - AIDS defining illnesses: CD4 <200
- Fastidious and some resistance to chlorine and filtration
- Found in 55% of SA surface water & 13% of treated potable water
- Infection may be acquired through
  - person-to-person transmission
  - animals (zoonotic transmission)
  - foodborne transmission
  - waterborne transmission

(Squire, S.A., Ryan, U. *Cryptosporidium* and *Giardia* in Africa: current and future challenges. *Parasites Vectors* **10**, 195 (2017))

Cryptosporidium parvum

- Most common diarrhoeal causing protozoa worldwide
- second only to rotavirus as a contributor to moderate-to-severe diarrhoeal disease during the first 5 years of life

- Seroprevalence of *Cryptosporidium* in Limpopo was found to be significantly higher (75.3%; 146 of 193) in HIV-infected individuals compared with student volunteers (32.8%; 19 of 58) ($P < 0.001$)[1]

(1. Bartelt LA, et al. High Anti-Cryptosporidium parvum IgG Seroprevalence in HIV-Infected Adults in Limpopo, South Africa. *The American Society of Tropical Medicine and Hygiene*. 2013.)

Non-infectious aetiologies of diarrhoea

- Drugs
  - Protease inhibitors (Lopinavir > Atazanavir)
  - Dolutegravir*
- Malignancy
  - Lymphoma
  - Kaposi's sarcoma
- Inflammatory bowel disease
- Malabsorption syndromes

(*<1% DTG diarrhoea in clinical trials)

Non –infectious diarrhoea in HAART era

Table 1. Incidence of Treatment-Related Grade 2–4 Diarrhea in Head-to-Head Comparisons of Boosted Protease Inhibitor Regimens Compared With Lopinavir Plus Ritonavir

Study	Patient Population	Patients, No.[b]	Patients With Grade 2–4 Diarrhea, %[a]		*P* Value
			Boosted PI/r	LPV/r	
			ATV/r		
BMS-045 [12, 13][c]	Treatment experienced	347			
48 weeks			3	11	.01
96 weeks			3	13	<.01
CASTLE [14, 15][d]	Treatment naive	878			
48 weeks			2	11	NR
96 weeks			2	12	NR
			DRV/r		
TITAN [16, 17][e]	Treatment experienced	595			
48 weeks			8	14	NR
96 weeks			8	15	NR
ARTEMIS [18, 19][d]	Treatment naive	689			
48 weeks			4	10	<.01
96 weeks			4	11	<.001

A Practical approach to diarrhoea in PWH

History

- Duration, severity of diarrhoea. Previous episodes?
- Stool consistency: presence of mucous or blood
- Constitutional symptoms: Fever, night sweats, weight loss
- Drugs:
  - Protease inhibitors or Dolutegravir
  - Recent antibiotic use
- HIV control: Currently taking ARVs, last HIV Viral load and CD4
- Travel history, or from Cholera area?

Examination

- Hydration status:
  - thirst, dry mouth, sunken eyes, drowsiness/ confusion
- Blood pressure <90/60mmHg, pulse >100
- Temperature
- Other signs of TB (Adenopathy, chest signs etc.)
- Abdominal examination:
  - Tenderness in the left iliac fossa (suggestive of acute colitis)
  - Other features of generalized tenderness are non-specific
- Fundoscopy for features of CMV retinitis (hemorrhages & exudates)

Resuscitate

- oral rehydration solution or SSS:

Homemade sugar and salt solution (SSS)
½ level medicine measure of table salt
plus
8 level medicine measures of sugar
dissolved in 1 litre of boiled (if possible) then cooled water
(1 level medicine measure = approximately 1 level 5 mL teaspoon)

- If vomiting or signs of severe dehydration: for IV rehydration
  - Balanced crystalloid solution e.g. Ringers lactate or Normal saline
- Check potassium level and replace as needed

Features of colitis clinically?

	Large bowel diarrhoea (colitis)
History	Low volume, frequent stools Red and white cells or mucous Tenesmus
Examination	Pyrexia Left iliac fossa tenderness

Colitis features

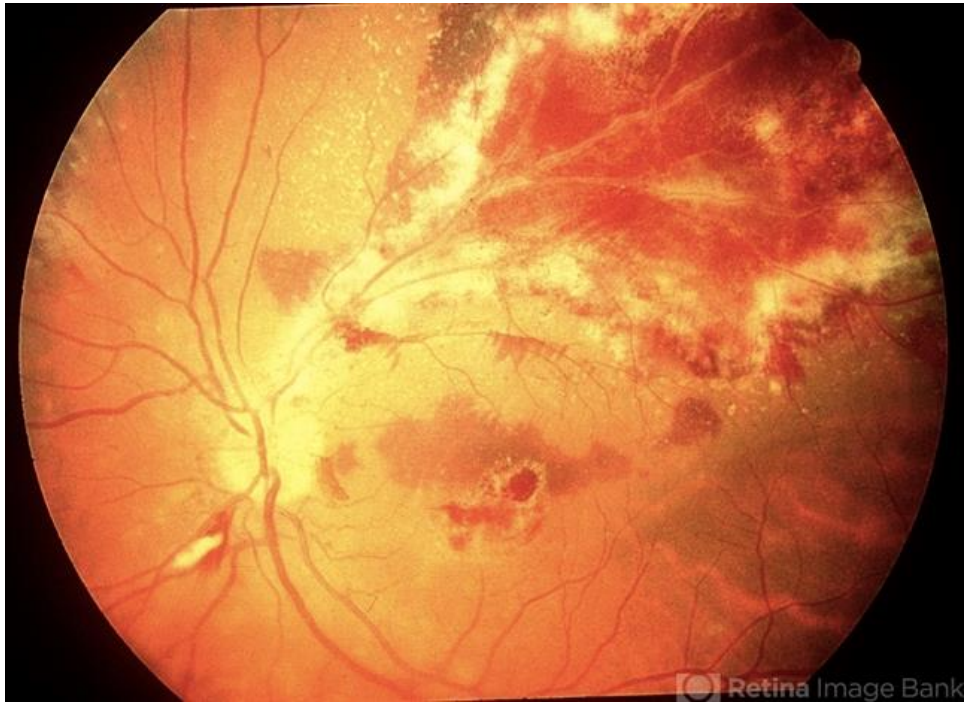
- Send stool m,c&s ± Blood culture
- Start empiric antibiotics
  - Ciprofloxacin 500mg po x 3/7 or
  - Ceftriaxone 1g ivi bd x 5/7
- Consider empiric metronidazole 800mg po x7-10/7 ONLY if in an amoebiasis endemic area
- Note if *C.diff* risks*: request *C.diff* tests on stool

***Risk factors for Clostridium difficle (C.diff):**

Older age
Hospitalisation – current or recent admission
Antibiotic exposure
    Especially broad spectrum antibiotics
    Current or within last 1-3 months
Cancer chemotherapy

Cytomegalovirus (CMV) colitis

- usually CD4 <50
- ? CMV retinitis on fundoscopy (may have visual disturbance)
- Can’t diagnose with blood serology or CMV viral load
- Need Flexible sigmoidoscopy & biopsy for ? CMV colitis



(https://imagebank.asrs.org)

No colitis features (enteritis)

- Acute diarrhoea (< 2 weeks)
  - Likely viral or less pathogenic bacterial cause
  - Continue iv or oral rehydration, and potassium supplementation as needed and monitor response
  - Anti-diarrhoeals if needed
  - monitor any potential drug cause

Chronic enteritis (> 2 weeks)

PHC guideline: HIV negative: consider empiric Giardia Rx: Metronidazole 2g/d x3

- stool for m,c&s + modified auramine stain
- Up to 3 stools if negative

Prominent night sweats, weight loss, or cough?

Yes: Add TB/MAC investigations & treat if positive/suggestive:
- Urine LAM
- Chest X-ray ± sputum GXP
- Abdominal Ultrasound
- TB Blood culture

Pathogen identified: Treat

No pathogen identified

If access to endoscopy:
Flexible sigmoidoscopy
Colonoscopy
Gastroscopy & duodenal biopsy
CT-Abdomen if above negative to exclude malignancy

No access to endoscopy:
Trial of empiric *Isospora belli* treatment
If no response, for ARV intervention as per *Cryptosporidium**
No response to above: refer for endoscopy

*** Cryptosporidium**
No effective specific treatment
Urgently initiate ARVs, or switch to second-line if failing or multiple defaults

Stool microscopy interpretation

Stool Analysis:

Appearance	Watery

Wet preparation:

Leucocytes	Occasional
Parasite(s)	NOT observed

Specimen processed after >24 hour delay. Please treat results with reserve.

Acid Fast Stain for Parasites:

Parasites	Cryptosporidium species observed

C.difficile GDH antigen and toxin test:

GDH Antigen	Negative
Toxin	Negative

Interpretation:
Clostridium difficile not detected

Bacterial Culture:

Pathogens excluded:

Salmonella species	NOT isolated
Shigella species	NOT isolated
Campylobacter species	NOT isolated
Yersinia enterocolitica	NOT isolated

Treatment of infectious diarrhoea (1)

Organism	Specific treatment
Protozoa	
Cryptosporidium	Nil
Isospora belli (cystoisospora belli)	Co-trimoxazole (80/400mg) 4 tabs 12 hrly x 10 days If allergic: Ciprofloxacin 500mg po 12 hrly x 10 days
Microsporidia spp.	Albendazole 400mg 12 hourly x 4 weeks
Giardia	Metronidazole 2g daily x 3
Amoebiasis	Metronidazole 800mg 8 hrly po x 10 days

Treatment of infectious diarrhoea (2)

Organism	Specific treatment
Bacteria	
Salmonella	Fluoroquinolone
Shigella	Fluoroquinolone
Campylobacter	Macrolide
Clostridium difficle	Metronidazole 400mg 8 hrly x 10-14 days Second line: Vancomycin 125mg 6 hourly po
Mycobacteria	
M.TB	Anti-TB therapy
M. avium-complex (MAC)	Azithromycin & Ethambutol
Viral	
CMV	Ganciclovir ivi

Endoscopy

- Useful for patients with non- resolving symptoms after negative initial stool analyses.
- Endoscopy with biopsy (histology, bacterial & mycobacterial culture & CMV PCR) yields an additional diagnosis in 30-70% of cases
- Which endoscopy route?
  - Colitis: Flexible sigmoidoscopy and proceed to full colonoscopy if inconclusive
  - Enteritis: Gastroscopy & duodenal aspirate/biopsy, or some recommend a higher yield with initial colonoscopy and terminal ileoscopy

Illustrative case

- 24 yo HIV+ male
- CD4 nadir 149
- Jan 2011:
  - Chronic diarrhoea
  - Isospora belli oocysts on stool
  - Treated Co-trimoxazole 4 tabs bd
  - Multiple relapses & admissions
- Sept 2011:
  - TDF/3TC/EFV initiated

- August 2012:
  - Unsuppressed VL
  - Switched to AZT/3TC/Atazanivir/ritonivir
- Jan 2013: CD4 416, VL log 4
- October 2013: CD4 459, VL <40 copies/ml
- Persistent diarrhoea, frequent hospital admissions
- Cotrimoxazole 4 tabs bd long term

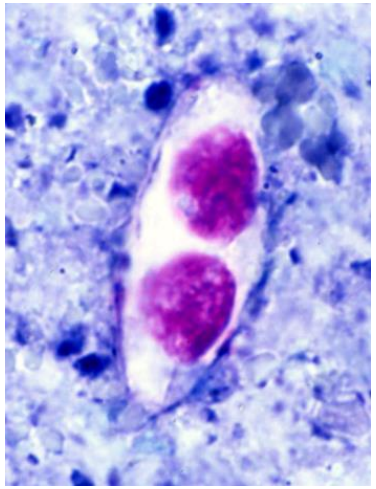
Re-admitted:

- Vomiting & diarrhoea
- Generalised weakness
- o/e:
  - Cachectic (Weight 38kgs)
  - Dehydrated
  - Abdo soft, a little distended

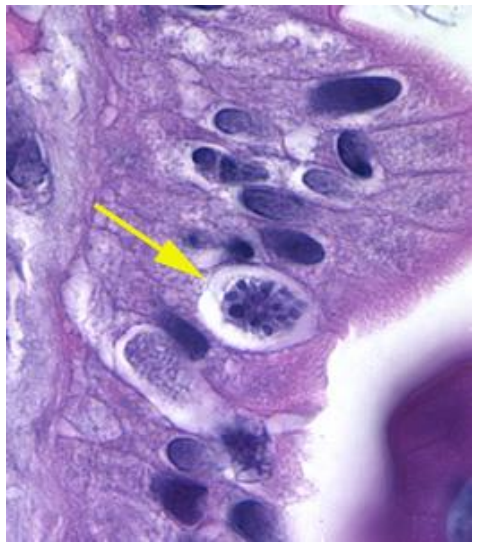
	Patient (mmol/l)	Normal ranges
K^+	2.5	3.3-5.3
Creatinine	60	60-120
Corrected Calcium	1.95	2.05-2.56
Magnesium	0.44	0.65-1.1
Phosphate	0.34	0.8-1.4
Albumin	20	35-55

Further investigations:

- Stool:
  - modified ZN stain:
    - Cystoisospora belli oocysts



- Gastroscopy duodenal biopsy:
  - Immature oocyst



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.

Table 1. Clinical summary of 8 patients with chronic isosporiasis despite immunological and virological response to ART.

Case number	1	2	3	4	5	6	7	8
CD4 nadir, cells/mm^3	32	210	281	52	221	215	141	71
Anti-retroviral regimens used	D3E/D3L/r	D3N/D3E/A3E	D3E	A3N	Tru At^r/.Tru L^r	D3E/.T3L^r	D3E	D3N
Maximum CD4 count while symptomatic, cells/mm^3 (duration of ART, months)	237(29)	1013 (60)	412 (6)	327 (24)	659 (48)	464 (17)	334 (25)	265 (23)
Any HIV viral load >50 copies/ml, (months of ART)	1000 (6)	None	86 (11) 400 (13)	None	2780 (10) 127 (48)	None	None	306671 (19)
Number of HIV viral load measurements <50 copies/ml §	3	7	2	10	8	5	2	3
Total duration of ART, years	4	5	2	7	5	3.5	2.3	2
Maximum secondary prophylaxis	CTX 1920 mg b.i.d. plus CPN 500 mg b.i.d.	CTX 1920 mg b.i.d.	CTX 960 mg b.i.d.	CTX 960 mg b.i.d.	CTX 960 mg b.i.d.	CTX 1920 mg b.i.d.	CTX 1920 mg b.i.d. plus CPN 500 mg b.i.d.	CTX 1920 mg b.i.d. plus CPN 500 mg b.i.d.
Hospital admissions for diarrhea n, (total days in hospital)	18 (151)	10 (60)	10 (81)	0	1 (8)	1 (7)	14 (71)	3 (18)
Stool samples*, n (% positive)	13 (54)	12 (8)	5 (40)	2 (100)	6 (50)	8 (50)	11 (9)	8 (50)
Duodenal biopsies, n (% positive)	3 (67)	3 (100)	3 (67)	1 (0)	2 (100)	0	3 (33)	1 (0)
Outcome	Died, complications of chronic diarrhoea	Died, complications of chronic diarrhoea	Died, complications of chronic diarrhoea	Symptoms resolved after 2 years. Currently well.	Persistent diarrhea and weight loss	Symptoms resolved after 2 years. Currently well.	Lost to follow-up presumed dead	Persistent diarrhea and weight loss. Now virologically suppressed

Potential mechanisms of refractory Isospora

- Poor GIT immune reconstitution
- Co-trimoxazole malabsorption & sub-therapeutic levels
- Co-trimoxazole resistance (?DHPS/DFTR mutations)
- Malnutrition immune suppression

Suggested therapeutic options:

- Co-trimoxazole 4 tabs 12 hourly for 1 month
- If clinical response, wean slowly (by 2 tabs/d every month)
- Alternative: Ciprofloxacin 500mg bd x 10-14 days

- Followed by Co-trimoxazole 2 SS tabs daily till CD4 >200 for >6months

- Weak evidence
  - Atovaquone
  - Nitazoxanide
  - Albendazole
  - Pyrimethamine

Case scenario 1

25 yo HIV+ male, CD4 150, ARV naïve presents with a 4 day history of watery diarrhoea. No vomiting, fever or LIF tenderness, normal vitals.

Do you?

1. Take a blood culture
2. Admit for IV ceftriaxone
3. Send home with oral ciprofloxacin & metronidazole x 5/7
4. Advise about oral rehydration & reassure
5. Prescribe loperamide

Case scenario 2

An ARV naïve HIV+ patient with a CD4 of 10 gets admitted with a fever of 38 deg, weight loss, and bloody diarrhoea for 2 weeks. Initial stools & BC negative, and no response to 5/7 IV ceftriaxone & metronidazole.

What is your next step?

1. Continue 2 weeks of Ceftriaxone
2. Repeat cultures & watch
3. Empiric TB treatment
4. Abdominal ultrasound
5. Flexible sigmoidoscopy & biopsy

Case scenario 3

40 yo male, HIV+ with a history of poor adherence on a TDF/FTC/EFV (TFE) regimen for > 5yrs. Admitted with 1 month diarrhoea, severely dehydrated. Hb 10. Stool auramine = “cryptosporidium”

Do you…?

1. Start Co-trimoxazole 4 bd
2. Restart his TFE regimen after taking a baseline VL
3. Start second line TDF/3TC/DTG
4. Discharge with loperamide to restart ARVs once diarrhoea settled
5. Give Albendazole x 1 month

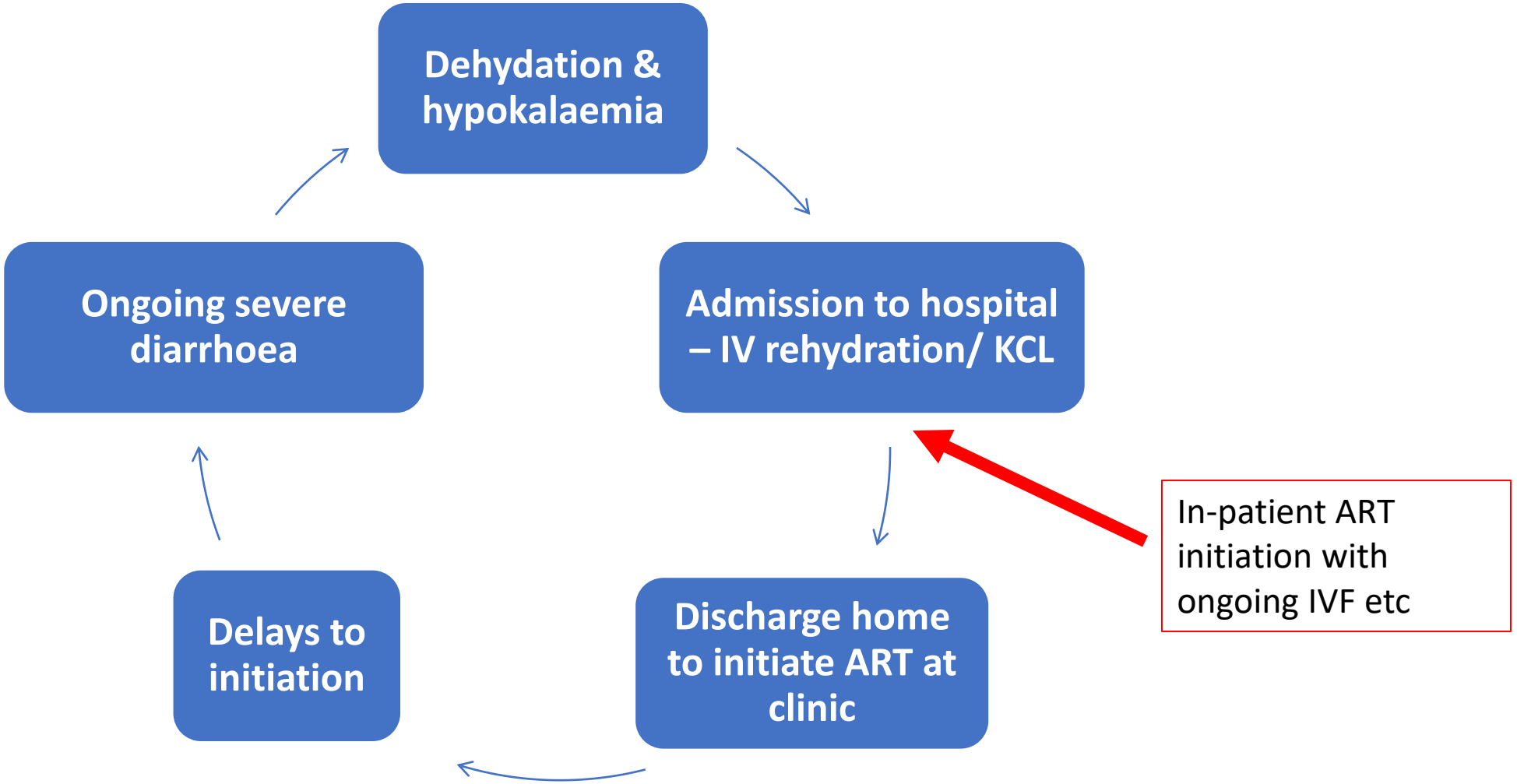
Case scenario 4

A 30 yo HIV+ female is referred to you due to non suppressed viral load (log 3). She has been taking AZT/3TC/Alluvia second line for 2 years, after failing TDF/FTC/EFV. She complains of daily diarrhoea, and admits to skipping morning doses when she needs to take a taxi into town.

Do you?

1. Tell her to try harder to take as prescribed
2. Send an HIV genotype resistance test
3. Switch to AZT/3TC/Atazanavir/ritonavir
4. Switch to TDF/3TC/DTG
5. Prescribe loperamide prn

Cryptosporidium ‘revolving door’



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