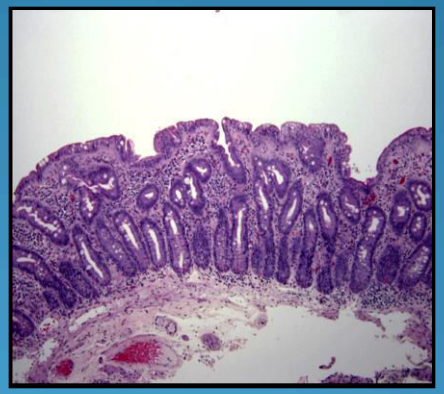
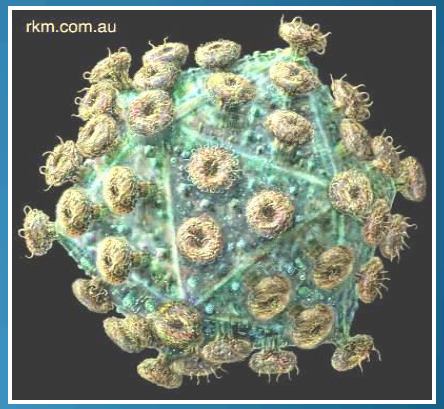
GUT FUNCTION & HIV PATHOGENESIS:

Nutritional Implications





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GIT & HIV PATHOGENESIS

- **GIT dysfunction** has been recognized as a **major manifestation** of **HIV** infection, since the earliest recognition of the acquired immune-deficiency syndrome (AIDS).
- It was originally thought, that this disease manifestation was considered to be sequelae of the immune destruction, that characterizes AIDS, ***rather than it being central to the pathogenesis of AIDS***. [1]

GIT & HIV PATHOGENESIS

- In the past decade, it has been observed that the **mucosal immune system and the intestinal immune system** are **pivotal in the pathogenesis of AIDS**, with the **most critical events**, namely:
  - **Transmission,**
  - **Viral amplification,**
  - **$CD4^+$ T-cell destruction occurring in the gastrointestinal tract (GIT),**
  - **Breakdown of the mucosal barrier with consequent microbial translocation,**

  are considered to be **major drivers of AIDS progression**.[1]
- The **mucosal tissue** is not only a primary site of viral transmission, but also a **major site of viral replication, and $CD4^+$ T-cell destruction**, ***regardless of the route of transmission.***[1]

HIV Enteropathy

- GIT enteropathy in persons living with HIV (PLWH) can occur from the **acute phase** of infection, through **to advanced disease**.
- It is characterized by:
  - **diarrhoea**,
  - **increased GIT inflammation**,
  - **increased intestinal permeability** (up to ***fivefold higher*** than in healthy individuals),
  - **malabsorption of bile acid, and vitamin B_{12}**. [2]

HIV Enteropathy

- **Histologically**, the GIT enteropathy in HIV involves:
  - **inflammatory infiltrates of lymphocytes**
  - **damage to the GIT epithelial layer** (which includes villous atrophy, crypt hyperplasia and villous blunting).
- These **pathological changes may** occur in the **absence of any detectable bacterial, viral or fungal enteropathogens**, which are often associated with enteropathy.[2]

HIV Enteropathy

- Although the mechanisms that cause the abnormalities in HIV enteropathy, are poorly understood, it has been suggested that HIV has a "**virotoxic**" effect on the **enterocytes**.
- **HIV gp120** has been found to result in **increased concentrations of calcium** in the **enterocytes**, which is associated with tubulin depolymerisation, and a **decrease in epithelial cells' ability to maintain ionic balances**. [2]

HIV Enteropathy

- **Local activation of GIT immune system**, is also thought to play a role in HIV enteropathy.
- In HIV there are **high levels of proinflammatory mediators** such as beta chemokines interleukin-6 (IL-6), interleukin-10 (IL10) and interferon (IFN-γ) found in the **lamina propria of the colon** in PLWH.
- The **degree of inflammation** has been found to correlate with the **level of viral replication**.
- Although systemic immune activation is a hallmark of HIV, the etiology of the latter remains elusive. [2]

HIV Enteropathy

- It has also been postulated that **local bacterial translocation across the damaged tight epithelial barrier**, results in **microbial products that stimulate the immune system locally**, presumably through receptors such as Toll-like receptors.
- A crucial consequence of induction of local inflammation through any means, is through **HIV's preferential infection of activated CD4$^+$ T-cells**, which in turn augments the HIV replication.[2]

$CD4^+$ T-cell Destruction

- **Originally it was thought that HIV involved a period of latency**, however, it is now well established **HIV attaches to the $CD4^+$ molecule on the T-cells** and the monocyte and macrophage lineage cells, and on a chemokine receptor, **during acute infection**.
- The direct infection of $CD4^+$ T-cells **leads to the destruction of these cells** and **global immune deficiency**, as these cells are required for induction and control of most immune responses.
- The infection of the monocyte and macrophage lineage cells, appears to be particularly important in **chronic HIV infection**, and are possibly **major reservoirs for viral replication and persistence**, and hence contributing to immune deficiency. [1]

$CD4^+$ T-cell Destruction

- More recently, it has been observed that the $CD4^+$ T-cells which bear the **CCR5 HIV co-receptor**, are the **primary targets of HIV**.
- The $CD4^+$ T-cells with CCR5 receptors constitute the majority of the $CD4^+$ T-cells. It is estimated that nearly **80%** of the **T-cell population**, are **found in the GIT.**[3]
- **Depletion of the $CD4^+$ T-cells** involves the **entire GIT**. [2]
- **Significant depletion** of these cells occurs in the **first 17 days post HIV infection**, and in a recently postulated model (based on GIT biopsies), it is thought that the **bulk of $CD4^+$ T-cell depletion occurs in the first 2 to 3 weeks of acute infection.** [3]

$CD4^+$ T-cell Destruction

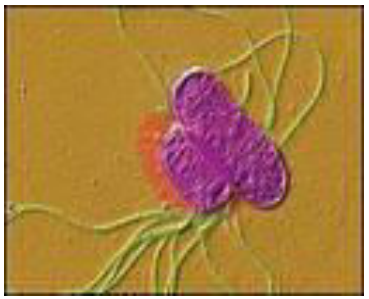
- PLWH with a **CD 4 count of less than 200 cells/uL**, have been found to have a **twofold increase in diarrhoea.**
- The latter affirms the view that diarrhoea is an AIDS defining condition.
- A **decrease in $CD4^+$ T-cells** (less than 200 cells/ uL) has been observed to be associated with **intestinal parasite infection** (for example: *Cryptosporidium, I belli & S. Stercoralis*), and with a higher incidence of diarrhoea.[4]

Th17 Cell Loss and Impairment of Mucosal Integrity

- **HIV mediated loss of Th17 cells** from the gut-associated lymphoid tissue (GALT) has been observed to **impair mucosal integrity**, and **innate defense mechanisms against gut microbes.**
- Th17 cells are important for **intestinal homestasis**.
- Th17 cells are involved in **epithelial regeneration**, and stimulate the production of defensins and mucin, as well as induce the expression of claudins, which are components of epithelial tight junctions.
- The Th17 cytokine, interleukin-22 (IL-22) increases the production of the **lipopolysaccharide binding protein** (LBP) in the liver. [5]

Th17 Cell Loss and Impairment of Mucosal Integrity

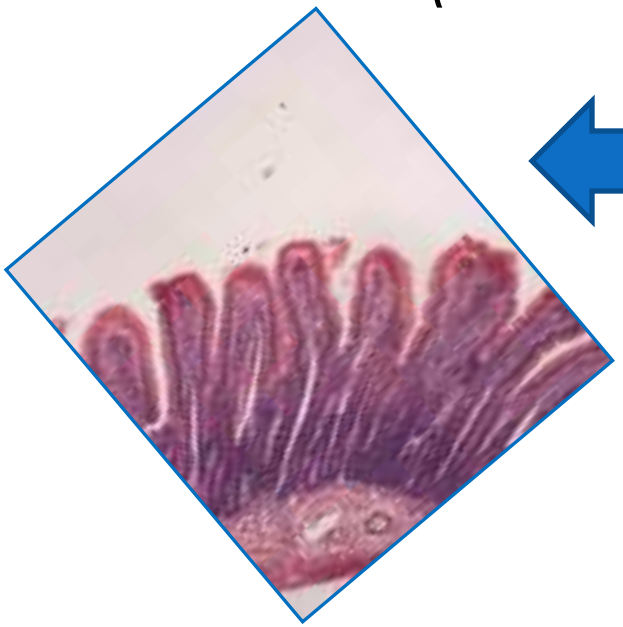
- Considering, the massive $CD4^+$ T-cell depletion in the lamina propria after HIV infection; it is **probable that Th17 cells are also depleted by HIV**.
- Th17 cells have multiple roles in controlling epithelial integrity and microbial invasion, the **depletion of Th17 is likely to affect the integrity of the GIT**.



- To date, **Salmonella** has been directly shown to **translocate across the GIT barrier**, when **Th17 cell function is compromised in the GALT**, in PLWH. [5]

Structural Villus Changes

- In PLWH with AIDS, the **mean villus/ height and mean villus/ crypt ratios** have been found to be **significantly lower** than those in non-HIV infected (normal) controls. [6]



Healthy Villi

Structural Villus Changes

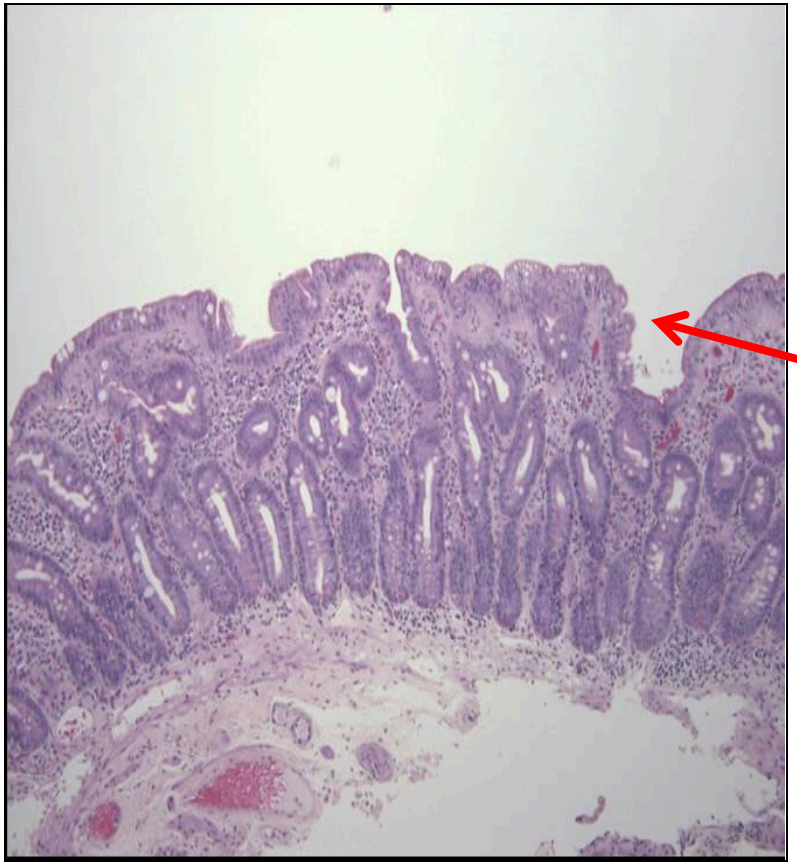


Figure 1.

- Biopsy of small bowel from a patient with AIDS and **pathogen-negative diarrhoea**.
- Note the prominent villus atrophy, crypt architectural distortion, decrease in crypt/villus ratio, and the significant influx of lymphocytes within the lamina propria.

Gastroenterology 2009, 136:1952-1955 JP Cello

Impact of HIV Infection on Lactose Absorptive Capacity

- It has been reported that **lactose malabsorption** is **significantly higher (70%)** in PLWH, than HIV-uninfected controls (34%).
- Furthermore, the **degree of lactose malabsorption** was found to be **significantly greater in PLWH with advanced disease**, versus those in the earlier stages of disease.
- The degree of lactose malabsorption has been found to be **related** to whether PLWH were **symptomatic and had intestinal manifestations**, than asymptomatic PLWH and non-HIV infected controls.
- It is presumed that apart from the presence of the HIV, other factors (probably both **structural and immune**), determine the enterokinetic alterations responsible for **lactase deficiency and lactose malabsorption**.[7]

Clinical Presentation of Enteropathy

- A high percentage of PLWH worldwide have been reported to **initially present or will develop diarrhoea**, irrespective of whether they are on HAART or not.
- In the United States, 50% of PLWH have presented with diarrhoea.
- However, in **developing countries** a prevalence of as many as **80%** of **PLWH** have **presented with diarrhoea**.
- The presentation of diarrhoea **may or may not** be in the **presence of an opportunistic infection of the GIT.** [6]

Clinical Presentation of Enteropathy

- **Clinical presentations** vary among PLWH with HIV-associated diarrhoea, **depending on the principal section of the GIT involved.**
- **Small bowel diarrhoea** tends to result in:
  - **large bulky postprandial stools** almost immediately after eating,
  - individual may experience postprandial paraumbilical **abdominal pain**.
  - if the affected **individual fasts, the diarrhoea significantly decreases.**
  - Individuals with small bowel diarrhoea usually experience **weight loss**. [6]

Clinical Presentation of Enteropathy

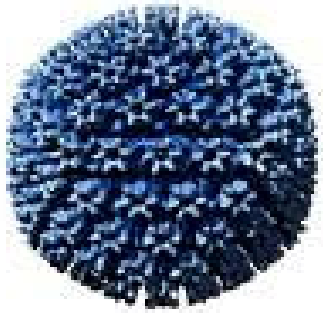
- Individuals with **large intestine diarrhoea** (termed "colitic diarrhoea"), usually present with:
  - **frequent, small-volume stools**, and the stools may have visible blood and mucus.
  - these individuals will usually experience **lower-quadrant abdominal pain, and the sensation of rectal urgency**.
- In many instances, it may be difficult to differentiate between small- and large bowel diarrhoea. [6]

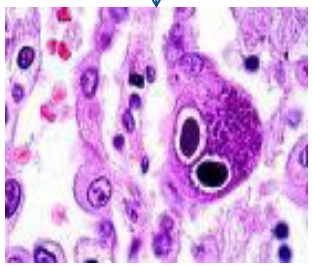
Clinical Presentation of Enteropathy

- The opportunistic infections that affect the GIT in PLWH include:
  - **parasitic infections -** for example: *Cryptosporidia, Isopora and Cyclospora*),
  - **viral -** in particular Cytomegalovirus {**CMV**},
  - **bacterial -**for example: Mycobacterium tuberculosis {TB}, Salmonella, Shigella, Campylobacter jejuni and Mycobacterium avium complex {**MAC**}. [6]

Clinical Presentation of Enteropathy

- **Prompt treatment of CMV is very important**, as it is associated with a **poor prognosis in PLWH** and a high rate of recurrence

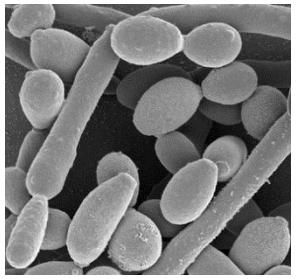


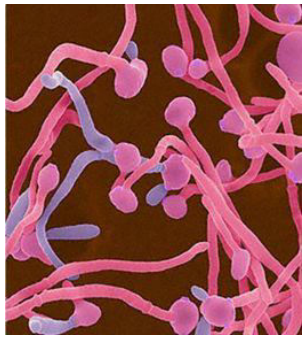


- **PLWH with GIT MAC usually have disseminated disease**, a very low $CD4^+$ T-cell count, and **limited survival time.**
- Since the **introduction of HAART**, the incidence and **prevalence of MAC has decreased**.
- TB of the GIT may affect immune-compromised and immune-competent individuals. [6]

Clinical Presentation of Enteropathy

- Opportunistic infections are not limited to the small- and large-bowel.
- May occur in the **upper GIT**, including :
  - **oesophageal pathology –**
    e.g.: ***candida oesphagitis, CMV,and herpes simplex virus,***
  - **Gastric and duodenal pathology**
    e.g.: ***CMV, Helicobacter pylori and cryptosporidium***.
- These infections may lead to **dysphagia** and hence **poor nutritional intake** but also ***recurrent dehydrating vomiting***. [8]





Clinical Presentation of Enteropathy

- Most of the **GIT opportunistic infections** will result in further aggravation of HIV-associated enteropathy, due to **structural damage and/ or immune sensitization**;
- Hence making it **difficult to differentiate** whether the severity of GIT related symptoms, is due to **HIV disease progression or the severity of other opportunistic infections**.

Accelerated GIT Transit Time

- In a recent study (2009),it was reported that HIV-infected children with a higher severity of malnutrition and more advanced stages of HIV clinical symptoms, had **accelerated whole gastrointestinal transit time**.
- **Early nutritional intervention for children with severe malnutrition** and advanced HIV disease, with **specialized lactose-free feeds with a low osmolality, to aid in delaying gastric GIT transit time**, and to allow for greater nutrient absorption, was recommended.[9]

The Role of Gut in HIV Disease Progression

- It has been speculated that due to the massive depletion of memory T-cells in the gut, as well as structural defects of the GIT lining, microbial translocation from the gut is probably involved in driving immune activation.
- It is thought that the **gut-derived microbes or microbial products translocate** to the systemic circulation in the absence of overt bacteremia. [3]

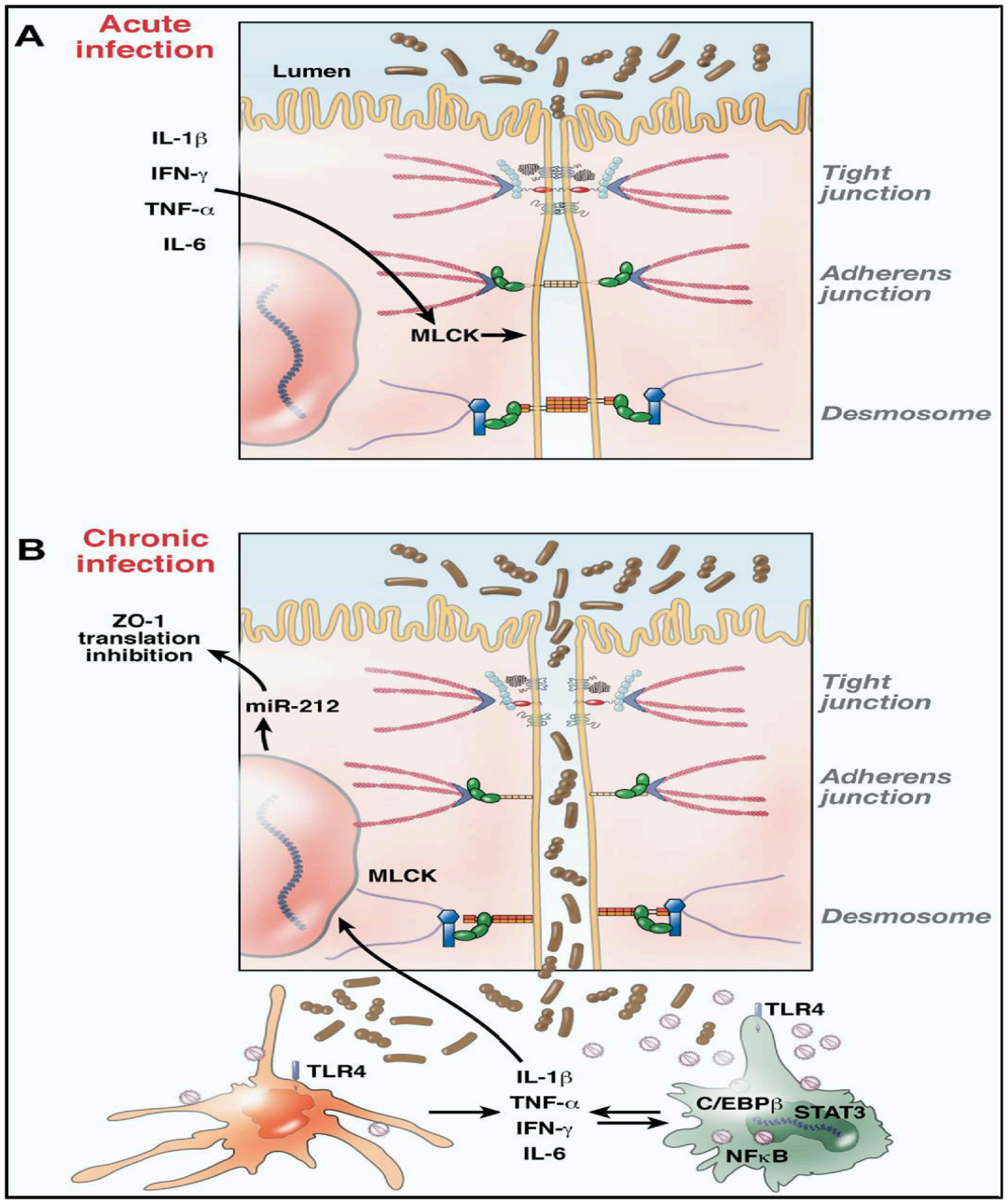


Figure 2:
Change in cell integrity, and bacterial translocation, in acute & chronic infection.

Quantification of Microbial Translocation

- Microbial translocation can be quantified by measuring **plasma levels** of **lipopolysaccharide (LPS),** the endoxin produced by bacteria that have translocated across the GIT lining.
- In PLWH with acute HIV infection, were found to have LPS levels similar to those of non-HIV infected individuals, however, in PLWH with **chronic HIV infection, the LPS levels were significantly higher**. [3]

Quantification of Microbial Translocation

- In an earlier study, in which non-infected HIV individuals were injected with LPS, with a resultant plasma level of LPS as low as **14pg/ml, that produced systemic immune activation with increased levels of inflammatory cytokines** (for example, tumour necrosis factor, interleukin (IL)-1 receptor antagonist, IL6 & IL8).
- In studies on **PLWH with chronic infection**, the **LPS levels** were found to be **75pg/ml**; hence sufficient to stimulate systemic immune activation. [3]

Quantification of Microbial Translocation

- It is well known that **immune activation decreases with potent antiviral therapy** (ART), although the decline is much slower than HIV RNA levels, and may remain elevated for a year after ART.
- It has been observed that statistically **significant decreases in LPS levels only occur** in PLWH, **after 48 weeks on ART**.
- It appears that **ART** is currently the **most effective way to protect the gut,** and help **reduce bacterial translocation,** and hence **reduce chronic systemic immune activation**.[3]

HAART and the Gastrointestinal Tract

- Currently **ART** has in most cases, been found to **reduce plasma viral loads to undetectable levels**, resulting in subsequent **increases in peripheral blood CD4$^+$ T-cells**.
- Early studies of HIV-associated enteropathy after the initiation of ART, showed significant decreases in GIT symptoms, namely, abdominal bloating and cramping, and loose stools.
- However, **a decrease in viral replication and CD4$^+$ T-cell reconstitution**, does **not occur** at a **similar rate at all anatomic sites**, **especially in the GIT**.[2]

HAART and the Gastrointestinal Tract

- Recent studies have shown that in the **small bowel CD4$^+$ T-cell reconstitution was poor**.
- PLWH with **acute HIV infection** who had been on highly active antiviral therapy (HAART), had a much **greater reconstitution (twofold) of CD4$^+$ T-cells compared** to individuals with **chronic HIV infection.**
- Importantly, it was also observed that although many PLWH treated with HAART reconstituted peripheral CD4$^+$ T-cells, but **no HIV-infected individual ever reconstituted GIT CD4$^+$ T-cells to levels observed in non-infected individuals**.[2]

HAART and the Gastrointestinal Tract

- **GIT CD4⁺ T-cells** have been observed to **still produce HIV virus, even years** after the initiation of HAART.
- Although the GIT is well vascularised, and ART drugs should be bioavailable; **high levels of multidrug-resistant proteins**, also named, "**toxin pumps**" (such as P-glycoprotein), are expressed on the apical **surface** of columnar **epithelial cells of both the small and large intestine**.
- It is speculated that these multidrug-resistant proteins, have specificity for protease inhibitors and nucleoside analogs, and **may reduce the local concentration of ART drugs to infected cells in the GIT**.
- Hence, allowing the **virus to slowly replicate and limit reconstitution of CD4⁺ T-cells**. [2]

HAART and the Gastrointestinal Tract

- Recently findings, also suggest that the **fibrotic deposition of collagen** also occurs in the **GIT Peyer's patches**, even during the acute phase of HIV infection.
- The **degree of architect damage of the Peyer's patches**, **predicts GIT CD4$^+$ T-cell depletion after HAART.**
- Although **HAART reduces GIT immune activation**, it is thought that the **ability of remaining** (but damaged) **lymphoid to support significant CD4$^+$ T-cell reconstitution**, is **permanently damaged**.[2]
- As many as **30%** of **PLWH on HAART**, **fail to reconstitute CD4$^+$ T-cells, despite HIV-viremia control**, and are described as immunologic-nonresponders (INRs). **INRs have an increased risk of HIV/ AIDS progression**.[11]

Plasma Citrulline: A Biomarker of Enterocyte Mass in PLWH?

- **Plasma or serum citrulline** essays have recently emerged as the **best tool in assessing enterocyte mass**, irrespective of the etiology of the intestinal mucosal disease.
- Citrulline is the **metabolic product of glutamine, and its related amino acids, and arginine**, and is **specifically synthesized** by **small bowel enterocytes**.
- Citrulline has been **validated for quantitative enterocyte assessment** in **villous atrophy disease**.[12]

Plasma Citrulline: A Biomarker of Enterocyte Mass in PLWH?

- Citrulline remains **uninfluenced by**
  - **nutritional status,**
  - **level of hypoalbuminemia,**
  - **or inflammatory status**.
- The **only limitation** is **significant renal failure** (creatinine clearance of < 30ml/min), because citrulline is metabolized into arginine in the proximal convoluted tubules in the kidneys. [12]

Plasma Citrulline: A Biomarker of Enterocyte Mass in PLWH?

- In a recent study (2009) it was found that plasma citrulline essays were a **reliable indicator of severe chronic infectious enteropathy in PLWH**, and hence a **reliable predictor** for the **indication for parenteral nutrition (PN)** for such cases.
- A **low citrulline level of <10umol/L** is considered an **indication for PN**.
- Whilst for an individual with a citrulline level of **>10umol/L, enteral route nutrition** supplementation is recommended. ***Normal citrulline levels = 40umol/L***.
- Citrulline is easy to measure through ion-exchange or reverse-phase liquid chromatography, which can usually be **performed in most hospital biochemistry laboratories**. [12]

The Role of HIV Vaccines in Enhancing GIT Mucosal Cell Immunity

- There is some promising evidence that suggests that **direct surgical introduction** of a **vaccine** (replication-competent recombinant adenovirus {**rAd**} vectors, specifically rAd5), rather than oral gavage, results in **100-fold higher transgene expression**, and which **stimulates potent CD8$^+$ T-cell responses** in the **intestinal and systemic compartments**.
- These responses could be further enhanced through intramuscular rAd5 injections.[13]
- The **activation status of CD8$^+$ T-cells** is considered to be one of the **best predictors of HIV disease progression**.[5]

New Therapies: Gene modification

- The safety & tolerability of infusions of lentiviral vector modified autologous CD4 T cells (VRX496-T) in HIV pts with controlled viremia were demonstrated.
  - ***Gene modified cells were shown to exert genetic pressure on HIV-1.***

Tebas P et al, Blood, 2013

New Therapies: Bovine immunoglobulin

- Oral serum bovine immunoglobulin improves duodenal immune reconstitution & absorption function in RVD pts with HIV enteropathy
  - 2.5g x 2 times daily for 8wks
  - **SBI significantly increased intestinal mucosal CD4 lymphocyte counts, function & showed evidence of intestinal repair in pts with HIV enteropathy**.

Asmuth DM, et al, AIDS, 2013.

Role of Probiotics in *Gut Integrity & Immune function*…in HIV

- Modulate gut microflora by **inhibiting proinflammatory cytokines**,
- **Reduce gut permeability**,
- Stimulate mucosal immunity

  (Marchetti G et al, Clin Microbio Rev,2013).
- **Reduction in abdominal bloating & discomfort, and diarrhoea**,
- Antibacterial property/ **resistance to pathogenic bacteria,**
- **Essential vitamin synthesis**

  (Wilson NL et al, J Assoc Nurs in AIDS Care, 2013).

Role of Probiotics in *Gut Integrity & Immune function*…in HIV

- Probiotics may aid in **significantly reducing/ preventing oral candidiasis**,
- Use of probiotics as an adjunct therapy in HIV maybe:
  - **Low cost**
  - **Non-invasive**
  - **Effective intervention for treating HIV related Sx that impact on the quality of life.**

(Wilson NL et al, J Assoc Nurs in AIDS Care, 2013).

Probiotics in HIV - Evidence

- **Gonzalez-Hernandez LA et al (Nutr J 2012):**
  - DBRC trial pilot,
  - **Lactobacillus rhamnosus & Bifodobacterium lactis & prebiotic (10g inulin),**
  - 4 groups: probiotics, prebiotics, symbiotic (pre & probiotic) & placebo, Rx = 16wks
  - Subjects: ARV naïve, CD4 >350
  - Findings: Probiotic group:
    - **Significant increment of probiotic load**
    - **Significant decrease in harmful bacteria,**
    - **Significant decrease in interleukin 6 cytokine**

Probiotics in HIV - Evidence

- **Irvine SL et al, Nutr Research 2011**
  - **Probiotic yoghurt consumption – impact on GI Sx, productivity & nutritional intake PLWHA** – Mwanza, Tanzania
  - **Lactobacillus Ramnosus**
  - Subjects; 85 Rx grp, 86 Control (placebo) grp, **70% in both grp on ARV**, **average CD4 370**
  - Consumed yoghurt (200ml) x 4/ wk
  - Yoghurt made & supplied by established community kitchen

Probiotics in HIV - Evidence

- **Irvine SL et al, Nutr Research 2011**
  - **Outcomes – Probiotic grp:**
    - Median increase **2hrs/ day – capacity to work**
    - Decrease in febrile Sx by 1 dy
    - Subgrp on ARVs = ***less like to experience severe stomach/ abdominal pain*** vs control grp.
  - **Potential benefits**
    - **Community kitchen model** = economically feasible, effective means for an aspect of HIV intervention
    - Yoghurt = ***well tolerated***, also = improved nutritional intake & may help alleviate GI Sx related to HIV & ARVs

Probiotics in HIV - Evidence

- **Hemsworth JC et al, Gut Microbes, 2012 (pre-lim data – 1st phase)**
  - **Micronutrient supplemented probiotic yoghurt**
  - **RDBC trial** – 3 period (Ontario Canada),
    - Probiotic grp,
    - Vitamin (Vit A,C) grp,
    - Probiotic + Vitamin grp

    for 30dys with a 14 day washout
  - Subjects: n=21, ***varying CD4 (<200 to >500)***, on ARVs, **average wt= 70kg** (well nourished).

Probiotics in HIV - Evidence

- **Hemsworth JC et al, Gut Microbes, 2012 (pre-lim data – 1st phase)**
  - **Outcome (1st Phase):**
    - **Overall increase in CD4**
    - Average wt gain = **0,7kg**
    - All grps:
      - subjective ***increase in energy levels & ability to perform tasks,***
      - **yoghurt was well tolerated**.

Probiotics in HIV - Evidence

- **Consensus report – Pre- & Probiotics to combat enteric infections & HIV in developing world, Monachese M et al, 2011, Gut Microbes.**
  - Probiotics appear to ***support the maintenance of strong epithelia layer & stimulate innate immunity***, which acts as the 1st layer of defense against translocation of viral particles & bacterial pathogens.
  - **L rhamnosus GR-1 & Bifidobacterium bifidum** confer some **immunostimulatory activity** in children & adults
  - **L rhamnosus GG**
    - **most effective in reducing duration of diarrhoea**
    - Stimulates immunoglobulin Ig A production

Probiotics in HIV – Need for Caution

- Patients **may develop bacteremia** on Probiotics (e.g. case report of a 29yr old female on Lactobacillus rhamnosus).

(Wilson NL et al, J Assoc Nurs in AIDS Care, 2013).

- There is **limited evidence** re use of probiotics in HIV
- ***Further research is required to establish the efficacy & safety in HIV***
- Establish **ideal strain & dose & mode** (capsule vs enriched yoghurt), **stable in bile & able to withstand pH of stomach** & small intestines, **sufficient adherence to intestinal mucosa**.

Probiotics in HIV – Need for Caution

Imai K et al, Cell Mol Life Sci 2012 (Japan)

- Observed that **high butyric acid producing** bacteria may be involved in AIDS progression by reactivating the latent HIV provirus
- Invitro study
- Observed high butyric acid producing bacteria (***Fusobacterium nucleatum, Closteridium cochlearium, Eubacterium multiforme* {gut}**, and *Anaerococcus tetradius* {vagina}) could **promote gene expression of latent HIV-1**, thus making co-infection of these anaerobic bacteria one of the ***risk factors for promoting AIDS progression.***

Summary

- **Hand and food hygiene** are v. important.
- Consider **yoghurt/ maas or low lactose therapeutic feeds** in under weight PLWHA.
- A **low lactose therapeutic feed with MCT fat** will be better tolerated in a severely emaciated PLWHA (avoid high fat supplements).
- Consider **monitoring citrulline levels** in severely emaciated PLWHA.

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Thank you for your attention!