Effect of 12-week cART on Gut Mucosal Immunity and Microbiome in Primary HIV Infection (PHI)

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Introduction

The short-time effects of cART in PHI on mucosal immune and microbiome imbalances in the gastrointestinal (GI) tract are largely unknown

Materials and Methods

11 PHI subjects were studied at T0 and T12 weeks of cART and compared to 10 naive chronically-infected-individuals (C-Naïve). Structure and M1/M2 macrophage polarization (IHC) as well as microbiome (MiSeq Illumina) were studied on gut biopsies. Th17 and Treg cells were assessed in GI and PBMCs (flow cytometry). Gut integrity (E-cadherin) and peripheral inflammation (sCD14, IL-6) were measured in plasma (ELISA)

Results

Subject characteristics are presented in Table 1.

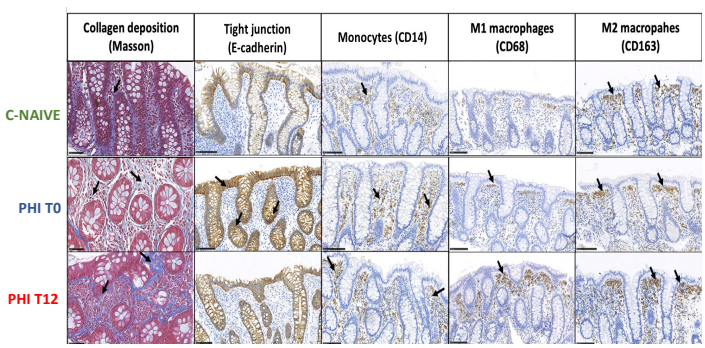
Table 1

Characteristic	PHI (N=11)	Chronic naive (N=10)	p-value
Age at diagnosis [years], median (IQR)	41 (29-45)	42 (34-51)	0.3408
Male sex, n (%)	11 (100)	8 (80)	0.2143
Ethnicity, n (%) Caucasian Other	 10 (91) 1 (9)	 7 (70) 3 (30)	 0.3108
Epidemiology, n (%) MSM Heterosexual/unknown	 10 (91) 1 (9)	 8 (80) 2 (20)	 0.5865
HBV/HCV coinfection, n (%)	3 (27)	3 (30)	1
Nadir CD4 [cell/mmc], median (IQR)	538 (493-609)	147 (12-279)	**0.0006**
CD4 count at colonscopy [cell/mmc], median (IQR) CD4% at colonscopy, median (IQR)	 538 (446-615) 25 (14-28)	 176 (94-279) 17 (10-18)	 **0.0008** 0.1295
HIV-RNA at colonscopy [log10 cp/mL], median (IQR)	5.58 (5.16-5.92)	5.13 (4.80-5.42)	0.058

In PHI, cART was introduced at 12, (IQR 9-24) days from PHI diagnosis and lead to viral decay (T0: log10 5.58cp/mL, 5.16-5.92; T12: log10 1.59cp/mL 1.56-1.73, p<0.0001) and CD4+ reconstitution (T0: 538/mmc, 446-615; T12: 756/mmc, 681-938, p=0.0003).

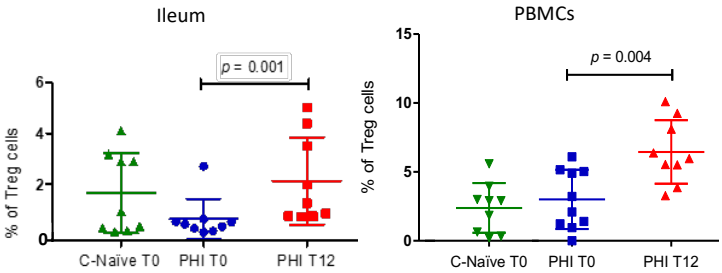
Collagen deposition, reduction of E-cadherin expression as well as migration of monocytes and M1/2 macrophages toward the gut lumen were found in untreated PHI. These features resembled those of C-Naïve, although less pronounced (Fig 1) and progressed at T12 regardless cART (Fig 1).

Figure 1. GI structure alterations and macrophage polarization



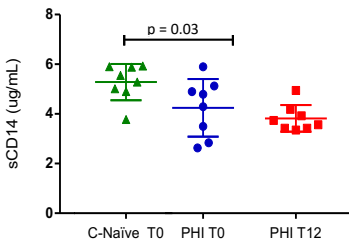
Untreated PHI and C-Naïve showed comparable Th17 and Treg cells in gut and PBMCs. In contrast, a significant increase of Tregs in ileum (T0: 0.43ug/mL, IQR 0.21-0.75; T12: 1.25ug/mL, IQR 0.75-3.95; p=0.001) and PBMCs (T0: 2.6ug/mL, IQR 1.16-4.69; T12: 5.9ug/mL, IQR 4.67-8.67; p=0.004) was observed (Fig 2).

Figure 2. Treg (CD4+CD25+CD127-) frequencies in ileum and PBMCs



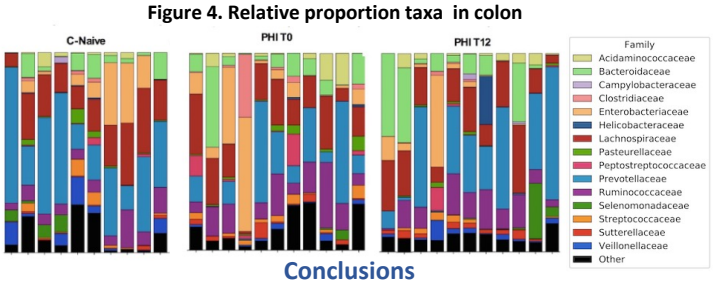
At T0, PHI showed lower plasma sCD14 (4.54ug/mL, IQR 3-5 vs 5.6ug/mL, IQR 5-5.9; p= 0.03) compared to C-naïve (Fig 3) as well as a trend to lower IL-6 and higher E-Cadherin. No significant changes were observed following cART.

Figure 3. sCD14 in plasma



At T0, PHI displayed high variability in gut microbiome composition which was markedly greater than that of C-Naïve. In PHI, cART determined a progressive decrease in gut microbial variability (Fig 4).

Figure 4. Relative proportion taxa in colon



Conclusions

Untreated PHI show gut damage with structural, and immune alterations, resembling those of C-Naïve, yet less pronounced. Untreated PHI also display lower systemic activation than C-Naïve. Short-term cART in PHI may hinder systemic immune activation, yet it appears to have little/no effect on gut alterations.