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Effects of *H. pylori* Co-infection on Immune Parameters in HIV-1 Patients in Ghana

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Abstract:

Background: Worldwide, there is a high co-endemicity of HIV and *H. pylori* infection. The objective of this study was to investigate the effect of *H. pylori* infection on clinical, immunological and virological parameters in HIV-positive individuals and uninfected controls in Ghana.

Method: Cross-sectional, observational study. Consecutive HIV-patients and HIV-negative blood donors were recruited at a university hospital in Kumasi, Ghana. *H. pylori* status was tested using a stool antigen test. Clinical and sociodemographic parameters, CD4 cell count, HIV-1 viral load were analysed. In addition, markers for T-cell activation and regulation were quantified by flow cytometry. Parameters were compared according to HIV and *H. pylori* status. The study was registered at Clinicaltrials.gov (NCT01897909). Recruitment for this has been completed, follow-up is currently on-going.

Results: The prevalence of *H. pylori* infection was significantly lower in HIV-infected (n=942) compared to HIV-negative (n=100) adults in Ghana (51.5% vs. 88%, p<0.0001). ART naïve HIV-patients with *H. pylori* co-infection (n=239) had higher CD4 cell counts (312 vs. 189 cells/µl, p<0.0001) and lower HIV-1 viral loads (4.92 vs. 5.21 log10 copies/ml, p=0.006) compared to those without *H. pylori* co-infection (n=255). In those patients, we also found lower proportions of CD4 T-cells with markers of immune activation (CD4+CD38+HLA-DR+; 22.55 vs 32.7, p=0.002), cell proliferation (CD4+Ki67+; 13.7 vs 25.3, p= 0.02) and immune exhaustion (CD4+PD-1+; 32.45 vs 40.00, p=0.005). *H. pylori* infection was not associated to more frequent gastrointestinal symptoms, anaemia or lower BMI. Having no access to pipe-borne water and higher CD4 cell counts were identified as risk factors for *H. pylori* infection. The use of antibiotics, including co-trimoxazole prophylaxis, was not associated with *H. pylori* co-infection.

Conclusion: HIV-infection was associated with a clearly lower rate of *H. pylori* co-infection. In ART-naïve HIV patients, *H. pylori* co-infection was associated with higher CD4 cell counts, lower HIV-1 viral loads and decreased markers of CD4 T-cell activation and exhaustion. Effects of *H. pylori* infection on systemic immune activation, as key factor in HIV pathogenesis, and on HIV disease progression warrant further investigation.

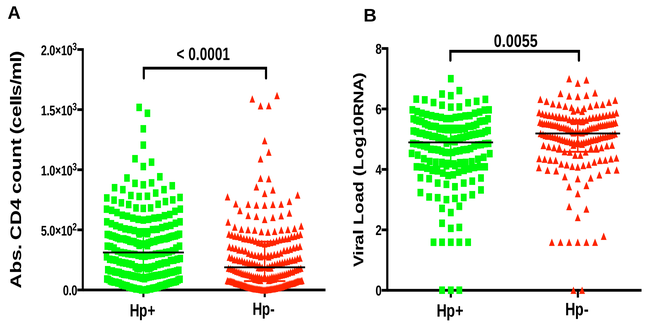

Figure 1. Absolute numbers of CD4 count and viral load in ART-naive HIV-1 patients in relation to *H. plyori* infection. CD4 and viral load (log10RNA) absolute numbers were compared between ART-naïve HIV-1 patients with *H. pylori*-Hp$^+$ and without *H. pylori*-Hp$^-$ in **(A)** and **(B)** respectively**.** Statistical analysis was performed using Mann-Whitney U test or unpaired student's t-test when comparing groups.

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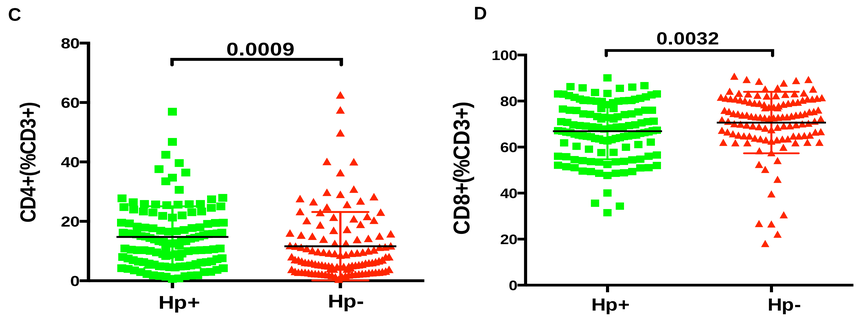


Figure 2. Frequencies of percentage CD4+ and CD8+ T cells in the peripheral blood of ART-naive HIV-1 patients in relation to *H. plyori* infection. Percentage CD4+ and CD8+ T cell frequencies were compared between Hp$^+$ and Hp$^-$ subjects in (**C**) and (**D**), respectively. Statistical analysis was performed using Mann-Whitney U test or unpaired Student's t-test when comparing groups.

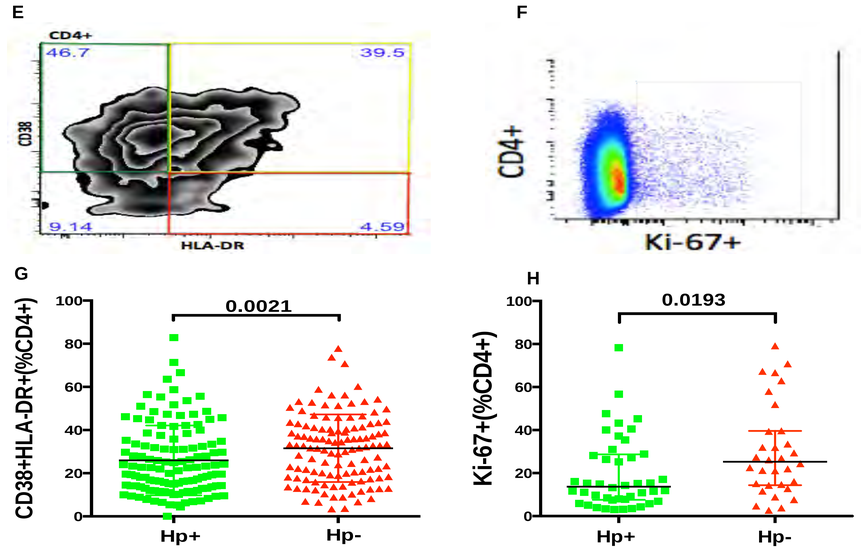


Figure 3. Frequencies of percentage immune activated CD4+T cells expressing the markers CD38, HLA-DR and cell cycle Ki-67 in the peripheral blood of ART-naive HIV-1 patients in relation to *H. plyori* infection. Representative zebra, dot plots and gating strategy for the detection of CD38+HLA-DR- (green), CD38+HLA-DR+(yellow) and CD38-HLA-DR+ (red) and Ki-67+ on CD3+CD4+ T cells are shown in (**E**) and (**F**) respectively. Percentage CD4+CD38+HLA-DR+ and CD4+Ki-67+ cell frequencies were compared between Hp$^+$ and Hp$^-$ subjects in (**G**) and (**H**), respectively. Statistical analysis was performed using Mann-Whitney U test or unpaired Student's t-test when comparing groups.

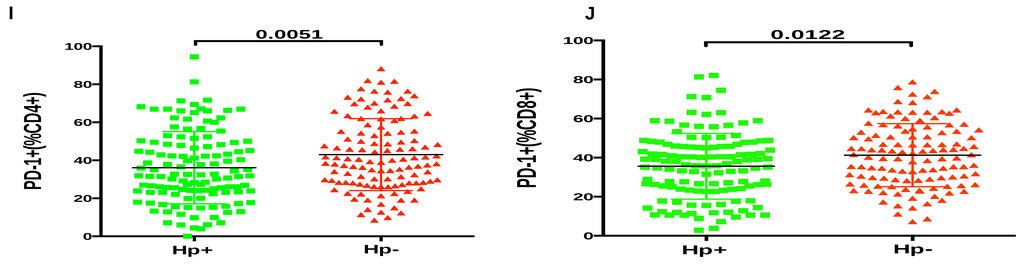
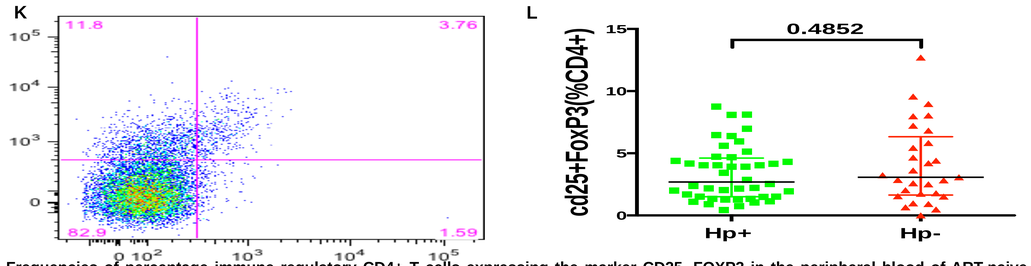


Figure 4. Frequencies of percentage CD4+ and CD8+ T cells expressing the apoptosis marker PD-1 in the peripheral blood of ART-naive HIV-1 patients in relation to *H. plyori* infection. Percentage CD4+PD-1+ and CD8+PD-1+ frequencies were compared between Hp$^+$ and Hp$^-$ subjects in (**I**) and (**J**), respectively. Statistical analysis was performed using Mann-Whitney U test or unpaired Student's t-test when comparing groups.



Frequencies of percentage immune regulatory CD4+ T cells expressing the marker CD25, FOXP3 in the peripheral blood of ART-naive HIV-1 patients in relation to *H. plyori* infection. Representative dot plot and gating strategy for the detection of CD25+FOXP3+ is shown in (**K**). Percentage CD4+CD25+FOXP3+ cell frequencies were compared between Hp$^+$ and Hp$^-$ subjects in (**L**). Statistical analysis was performed using Mann-Whitney test or unpaired Student's t-test when comparing groups.

Table 1. Immunological parameters according to H. pylori status

	HIV-positive treatment naive		HIV-positive on ART		HIV-negative	
Variable, median (IQR)	H. pylori positive, n=124	H. pylori negative, n=119	H. pylori positive, n=133	H. pylori negative, n=81	H. pylori positive, n=69	H. pylori negative, n=10
CD4+ cell count/µl	312 (135-484)	224 (79-426) *	505 (332-719)	448 (296-590)	958 (787-1169)	793 (737-980)
CD8+ cell count/µl	1186 (872-1739)	1326 (887-2034)	1462 (1092-2043)	1396 (1072-2072)	411 (304-548)	585 (412-811)
CD4+/CD8+ T cell ratio	0.34 (1.75 - 5.49)	0.19 (0.09-0.42) **	0.59 (0.41-0.93)	0.43 (0.32-0.81) *	2.22 (1.79-3.05)	1.77 (1.01-2.38)
Viral load, log10 c/ml	4.82 (4.09-5.43)	5.18 (4.57-5.67) **	1.59 (1.59-19)	1.59 (1.59-1.83)	NA	NA
HLA-DR+CD38+CD4+	22.55 (13.70-34.93)	32.70 (18.65-41.25) **	12.90 (7.30-20.60)	11.90 (7.76-18.90)	6.31 (4.94-8.15)	10.40 (8.67-15.15) *
Ki67+CD4+	15.10 (8.33-32.10)	26.80 (15.10-49.00) *	7.96 (5.48-12.00)	9.33 (6.98-13.50)	4.74 (3.75-5.73)	5.09 (4.26-6.51)
PD-1+CD4+	32.45 (23.33-48.73)	40.00 (28.35-55.30) **	31.80 (21.30-44.40)	31.70 (18.30-46.40)	30.90 (19.80-35.20)	35.95 (25.03-37.28)
CD57+CD4+	13.90 (9.39-25.73)	18.30 (9.70-29.50)	16.10 (9.32-26.90)	16.70 (10.00-30.30)	12.80 (8.16-24.50)	14.25 (11.25-39.78)
CD25+Foxp3+CD4+	2.54 (1.52-4.54)	3.28 (1.79-6.83)	1.83 (1.15-3.76)	2.44 (1.64-4.83)	1.59 (1.12-2.23)	1.46 (0.80-2.30)
HLA-DR+CD38+CD8+	49.25 (39.08-62.10)	52.90 (43.35-63.95)	27.90 (20.00-40.60)	26.00 (18.10-36.40)	18.70 (15.30-26.20)	34.85 (22.13-44.58) **
Ki67+CD8+	10.30 (7.88-15.90)	16.60 (11.20-23.10) *	6.04 (4.02-8.53)	9.27 (4.29-17.13)	4.58 (3.47-5.92)	5.19 (4.47-5.82)
PD-1+CD8+	36.15 (23.85-45.83)	41.50 (28.85-53.25) *	22.60 (14.50-34.80)	22.30 (16.10-32.80)	15.10 (9.57-20.40)	17.60 (6.48-23.175)
CD57+CD8+	44.85 (36.30-55.43)	45.80 (35.25-57.35)	54.40 (45.80-65.10)	52.80 (43.80-62.20)	60.00 (42.00-71.70)	66.65 (54.80-72.70)

*p<0.05; **p<0.01; ***p<0.001