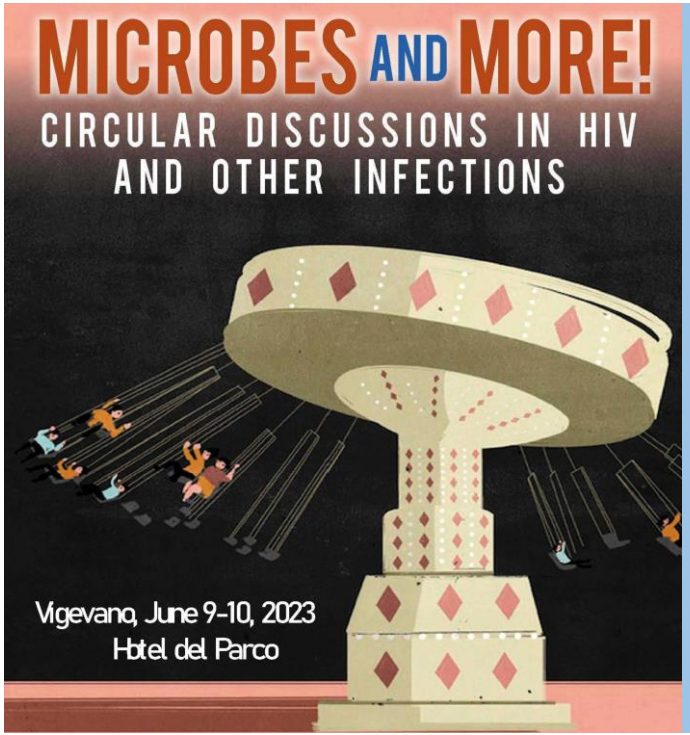

Effects of cART on residual inflammation and HIV reservoirs in Primary and Chronic HIV infection

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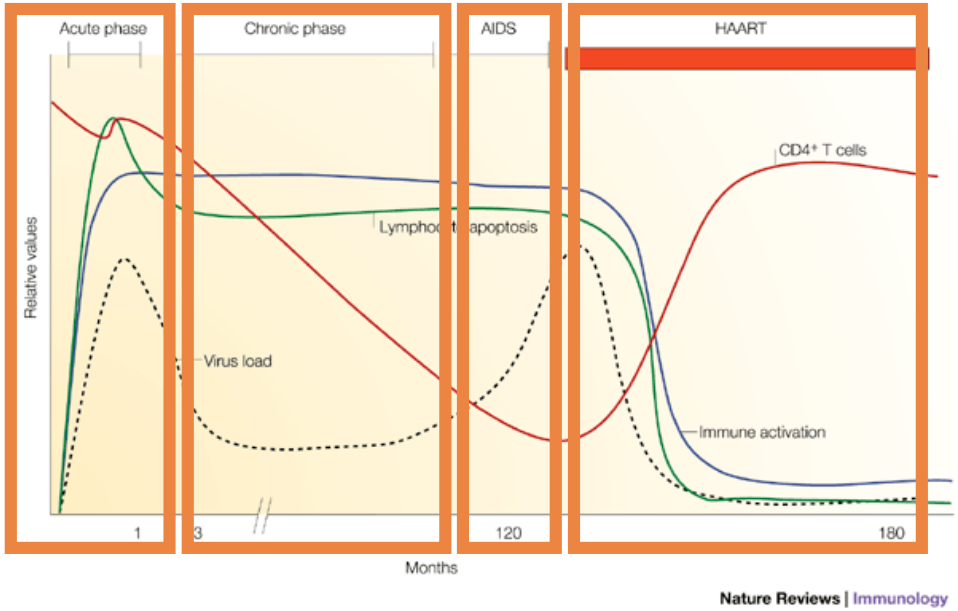
Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Background

In natural history, HIV infection involves:

- **P**rimary **H**IV **I**nfection, **PHI**
- **C**hronic **H**IV **I**nfection, **CHI**
- AIDS

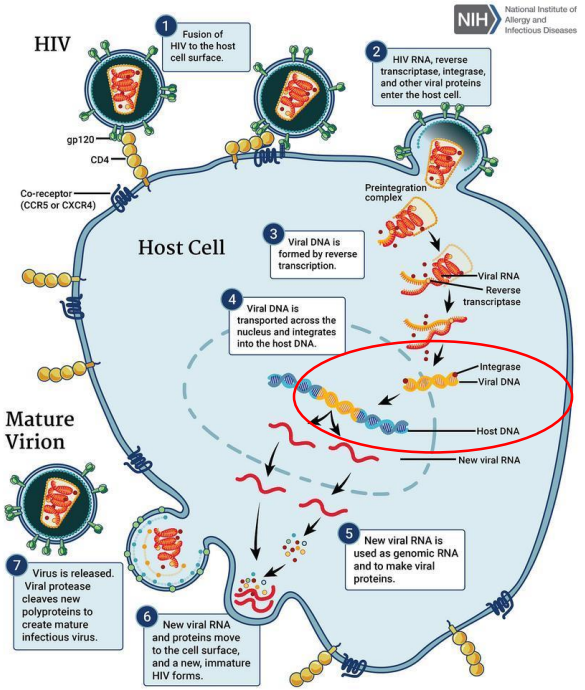
cART (*Combination Antiretroviral Therapy*) → **reduce viral load** and allow a **reconstitution of CD4+** T lymphocytes



Background

Primary HIV Infection → key pathogenetic moment for the establishment of **viral reservoir in cells and tissues**

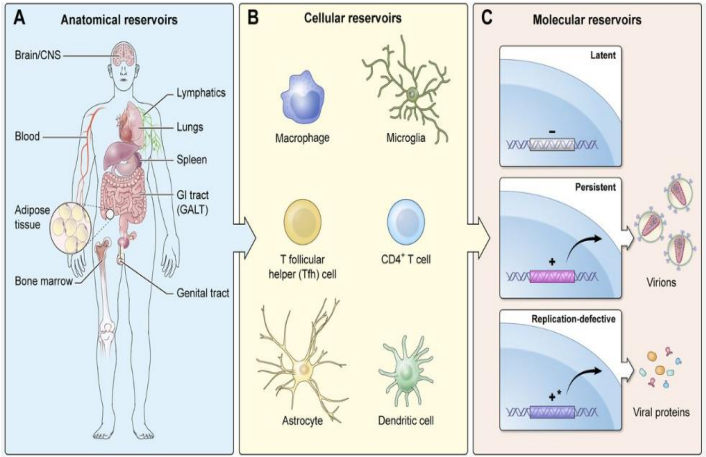
-Infected cells with latent proviral DNA
-Main obstacle to eradication and definitive cure



NIH, *National Institute of Health*

Background

- In the early stages of acute infection**, the viral reservoir** is established
- **High systemic inflammation** occurs during acute infection
- **Mutual interaction** between viral reservoir and inflammation during acute and chronic phases



Henderson LJ, *Journal of Virology*, 2020

- Correlation of inflammation and mortality

	Crude and adjusted relative hazards of new AIDS or non-AIDS Severe Events (SNAEs) or death in total population					
	Crude RH (95% CI)	*p*-value	Adjusted[a] RH (95% CI)	*p*-value	Adjusted[b] RH (95% CI)	*p*-value
(a) Biomarkers fitted as categorical variables						
LPS, pg/ml						
< =250.8	1.0		1.0		1.0	
> 250.8	0.85 (0.53, 1.36)	0.495	0.76 (0.46, 1.26)	0.292	0.88 (0.52, 1.49)	0.643
not measured	1.09 (0.72, 1.65)	0.681	1.11 (0.72, 1.73)	0.631	1.22 (0.77, 1.92)	0.400
sCD14, ug/ml						
< =2.83	1.0		1.0		1.0	
> 2.83	1.10 (0.77, 1.58)	0.586	0.95 (0.65, 1.39)	0.805	0.88 (0.59, 1.29)	0.504
not measured	1.26 (0.40, 4.03)	0.695	0.87 (0.26, 2.86)	0.819	1.44 (0.41, 5.02)	0.570
EndoCAb, MMU/ml						
< =36.5	1.0		1.0		1.0	
> 36.5	0.75 (0.52, 1.06)	0.107	0.82 (0.56, 1.19)	0.296	0.84 (0.57, 1.24)	0.378
not measured	0.22 (0.03, 1.56)	0.129	0.19 (0.03, 1.38)	0.100	0.18 (0.02, 1.40)	0.100
hs-CRP, mg/L						
< =1.51	1.0		1.0		1.0	
> 1.51	1.52 (1.01, 2.29)	0.044	1.47 (0.96, 2.26)	0.077	1.54 (0.99, 2.39)	0.056
not measured	1.19 (0.74, 1.93)	0.478	1.26 (0.76, 2.07)	0.369	1.28 (0.77, 2.13)	0.345

Merlini, Marchetti, *BMC Infectious Diseases*, 2021

Can early initiation of **cART** during ***P**rimary **H**IV **I**nfection* (**PHI**) play a role in **reducing inflammation and reservoir size**?

Materials and Methods

Study population

55 Individuals with ***P**rimary **H**IV **I**nfection* (PHI) from the **INACTION** (**I**talian **N**etwork of **AC**u**T**e HIV **I**nfect**ION**) cohort

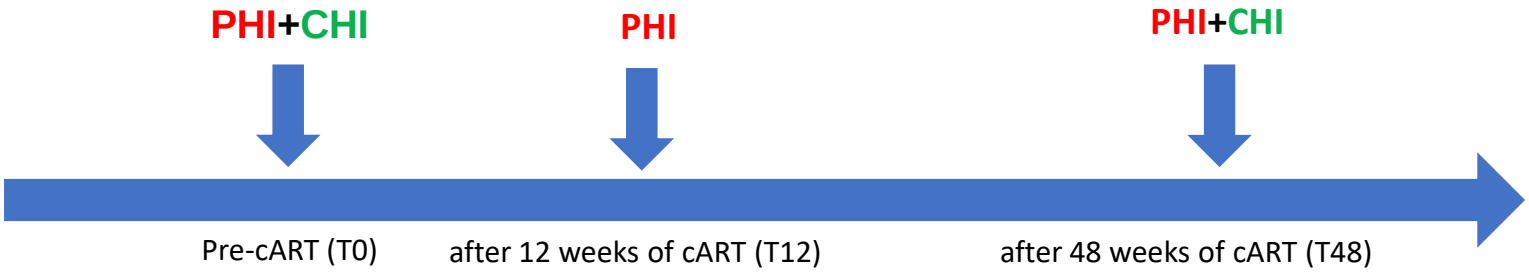
18 Individuals with ***C**hronic **H**IV **I**nfection* (CHI) from the **Clinic of Infectious Diseases and Tropical Medicine** of ASST Santi Paolo e Carlo, Department of Health Sciences (DISS), University of Milan

Plasma inflammation parameters

Peripheral HIV-1 DNA by Droplet Digital PCR (Biorad QX100), normalized to RPP30 reference gene

Pro-inflammatory cytokines: TNF-α, IFN-γ, IL-2, IL-4 (Luminex)

Microbial (sCD14) and gut integrity (E-cadherin, I-FABP) plasma markers (ELISA)



Statistics

PHI T0-T12-T48: Friedman test

CHI **T0-T48**: Wilcoxon signed-rank test

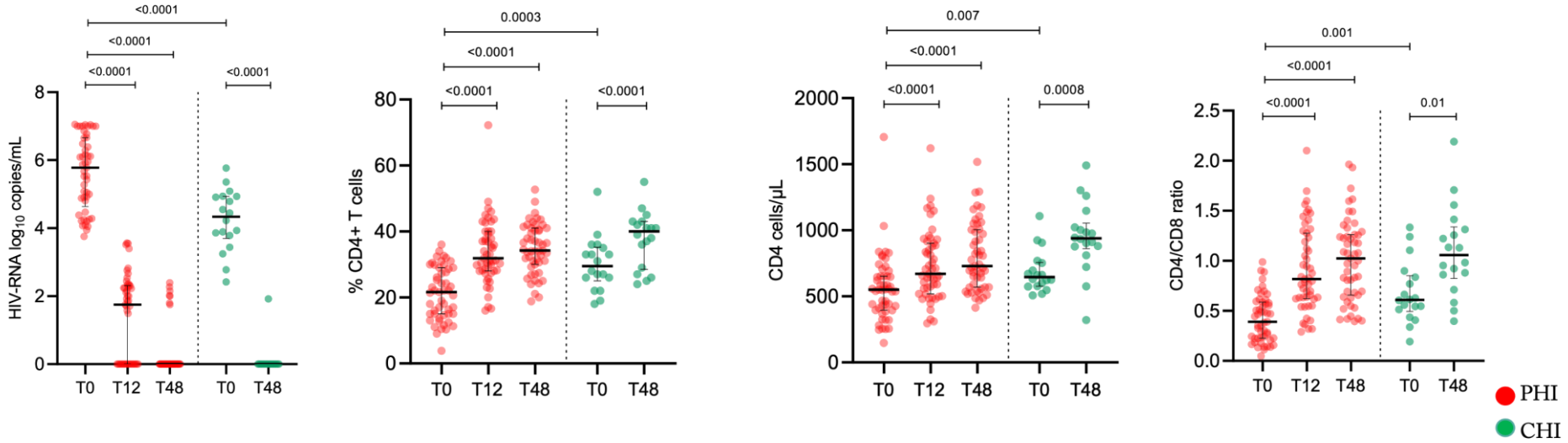
PHI-CHI (at T0 and T48): Mann-Whitney U test

Study population

	PHI T0 (n=55)	CHI T0 (n=18)	*P* value
Age, years, median (IQR)	34 (27-45)	31 (26-45)	0.6
Sex, n (%)			
Male	53 (96.36%)	16 (88.89%)	0.2
Female	2 (3.64%)	2 (11.11%)	
Previous AIDS diagnosis, n (%)	0 (0%)	1 (5.56%)	0.2
Viro-immunologic parameters, median (IQR)			
%CD4 at T0	21.6 (15-29)	29.5 (25-35.25)	0.0003
CD4 at T0, cells/µL	551 (395-653)	645.5 (576.3-756.3)	0.007
%CD8 at T0	53.1 (47.4-67.6)	46 (37-50.25)	0.001
CD8 at T0, cells/µL	1301 (836-2376)	986.5 (786.3-1558)	0.1
CD4/CD8 ratio at T0	0.39 (0.22-0.58)	0.6 (0.49-0.85)	0.001
HIV-RNA, copies/mL, median (IQR)	676722 (55375-4547657)	22534 (5262-86524)	<0.0001
Fiebig stage, n (%)			
I-III	19 (34.54%)	NA	NA
IV-VI	36 (65.45%)	NA	
cART regimen, n (%)			
INSTI-based (3DR)	20 (36.36%)	10 (55.5%)	
INSTI-based (2DR)	0 (0%)	3 (16.6%)	
NNRTI-based (3DR)	0 (0%)	5 (27.7%)	<0.0001
PI-based (3DR)	19 (34.54%)	0 (0%)	
INSTI + PI-based (4DR)	16 (29%)	0 (0%)	
HBsAg, n (%)	0 (0%)	0 (0%)	>0.9999
HCV, n (%)	2 (3.77%)	2 (11.76%)	0.2

Legend: *cART*, combination antiretroviral therapy; *INSTI*, integrase strand transfer inhibitor; *NNRTI*, non-nucleoside reverse transcriptase inhibitor; *PI*, protease inhibitor; **Statistical analyses*, Mann-Whitney U test, Fisher exact test, Chi-square test, as appropriate.

Viro-immunological parameters during cART in PHI and CHI

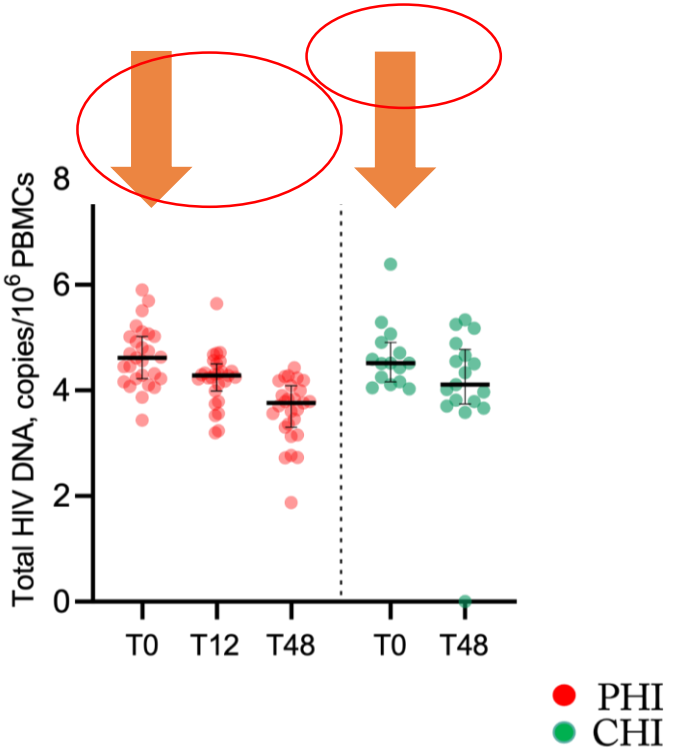


cART causes:

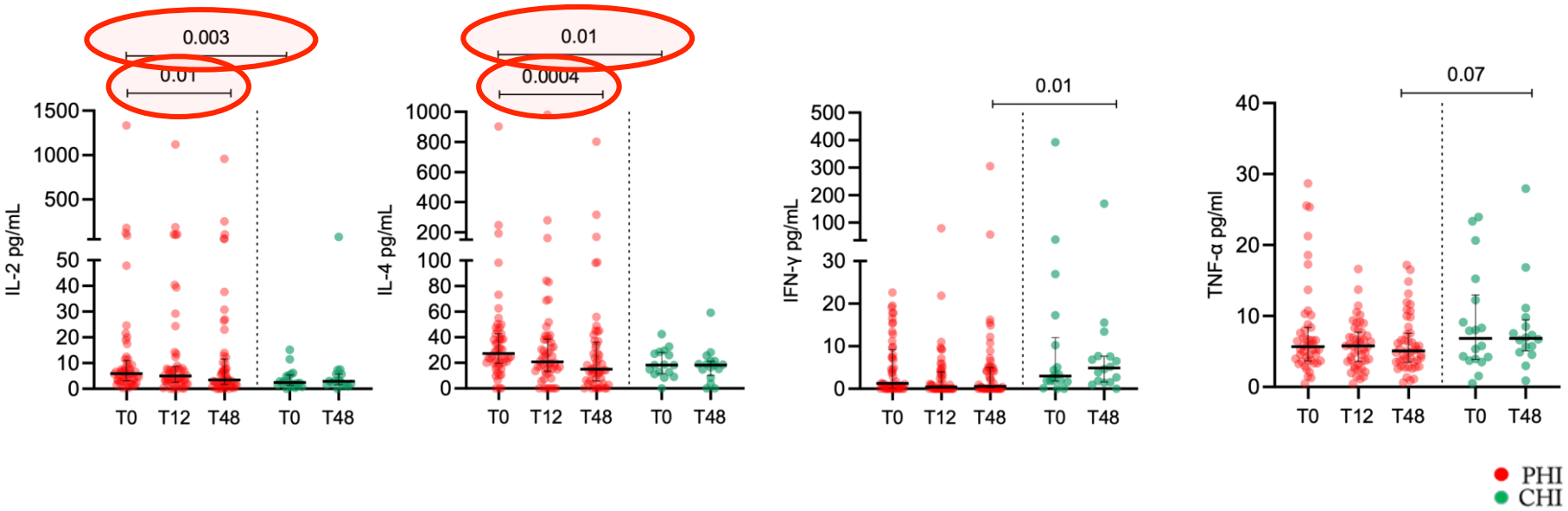
- a **reduction** in **plasma viremia**
- a **reconstitution of CD4+ T lymphocytes**, both in percentage and absolute terms
- an **increase in the CD4/CD8 ratio**

Reduction in HIV DNA during cART in PHI but not in CHI

- **PHI** and **CHI** have **similar levels** of **HIV DNA** at **T0**
- Significant **reduction** in **HIV DNA during cART** in **PHI**, but not in **CHI**
- Significantly **lower HIV DNA levels in PHI** than **CHI** at **T48**

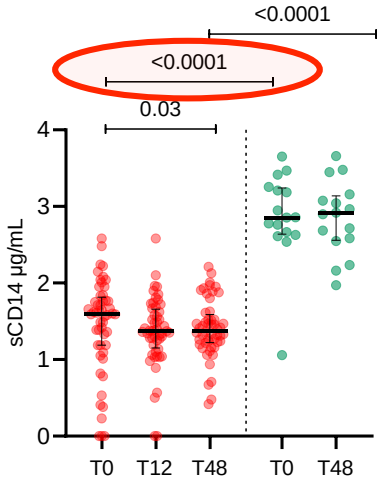


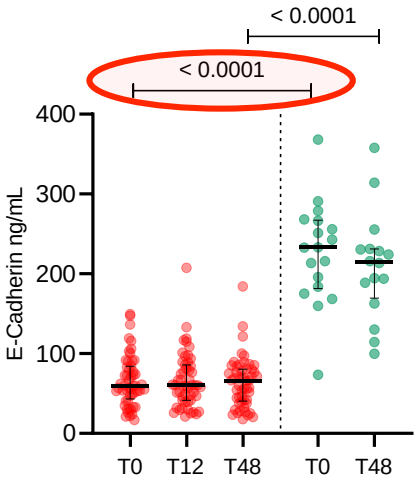
Reduction of inflammation in PHI during cART, but comparable levels to CHI after cART

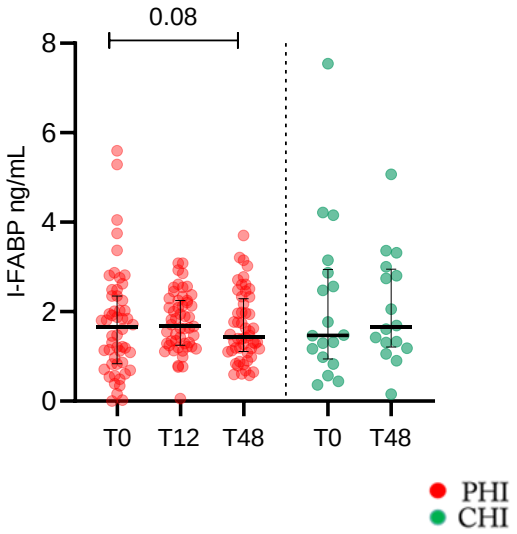


- **PHI** have higher levels of IL-2 and IL-4 at **T0**
- **Inflammation** is **reduced** only in **PHI** undergoing cART
- **Inflammation** levels are **similar** in **PHI** and **CHI**, with the exception of IFN-γ at T48

Lower levels of sCD14 and E-cadherin in pre-cART PHI than CHI







- **Lower** levels of **sCD14** and **E-cadherin** in **PHI** than **CHI** at **T0**
- **Reduction** of **sCD14** levels undergoing cART only in **PHI**
- **Lower** levels of **sCD14** and **E-cadherin** in **PHI** than **CHI** at **T48**
- Trend towards a **reduction of I-FABP** only in **PHI** at **T48**

Future Directions

- Experiments
- 1-3-β-D glucano, EndoCab, LBP (plasma)
- T-cells markers? Reservoirs, intact proviral DNA assay (PBMCS)

Conclusions

Early initiation **of cART** in **Primary Infection**:

↓ HIV reservoirs

↓ peripheral inflammation

↓ immune activation (sCD14)

Gut barrier damage:
↓ in PHI *vs* CHI (E-cadherin) → **Early initiation of cART**, during Primary Infection, **could limit intestinal damage and maintain intestinal homeostasis**

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