Impact of antiretroviral therapy on gut immunology and the HIV reservoir in “elite controllers”

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CHANGING THE COURSE OF THE HIV PREVENTION, ENGAGEMENT AND TREATMENT CASCADE

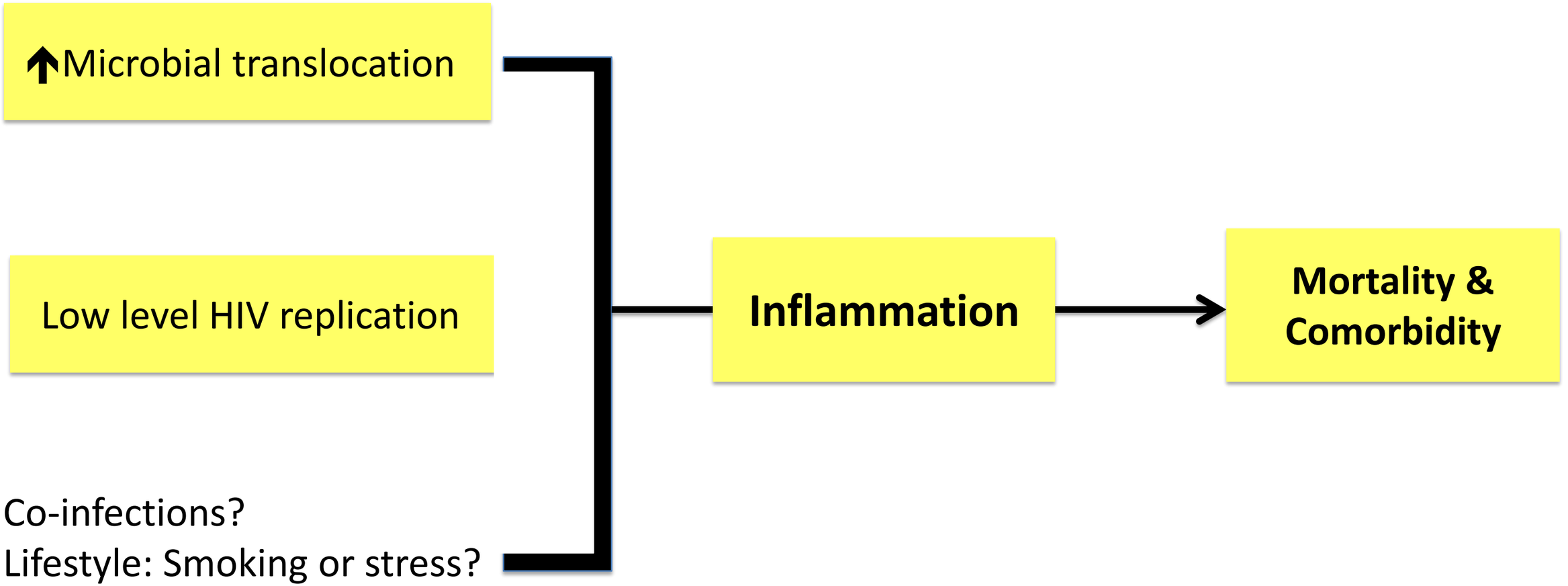
HIV “Elite Controllers” (EC)

- Rare group of HIV-infected individuals (<1%) who suppress HIV in the absence of antiretroviral therapy (Hubert, AIDS 2000)
  - Relatively normal CD4 count, although some experience CD4 decline (Okulicz, JID 2009)
  - Viral load <50 copies/ml without ART

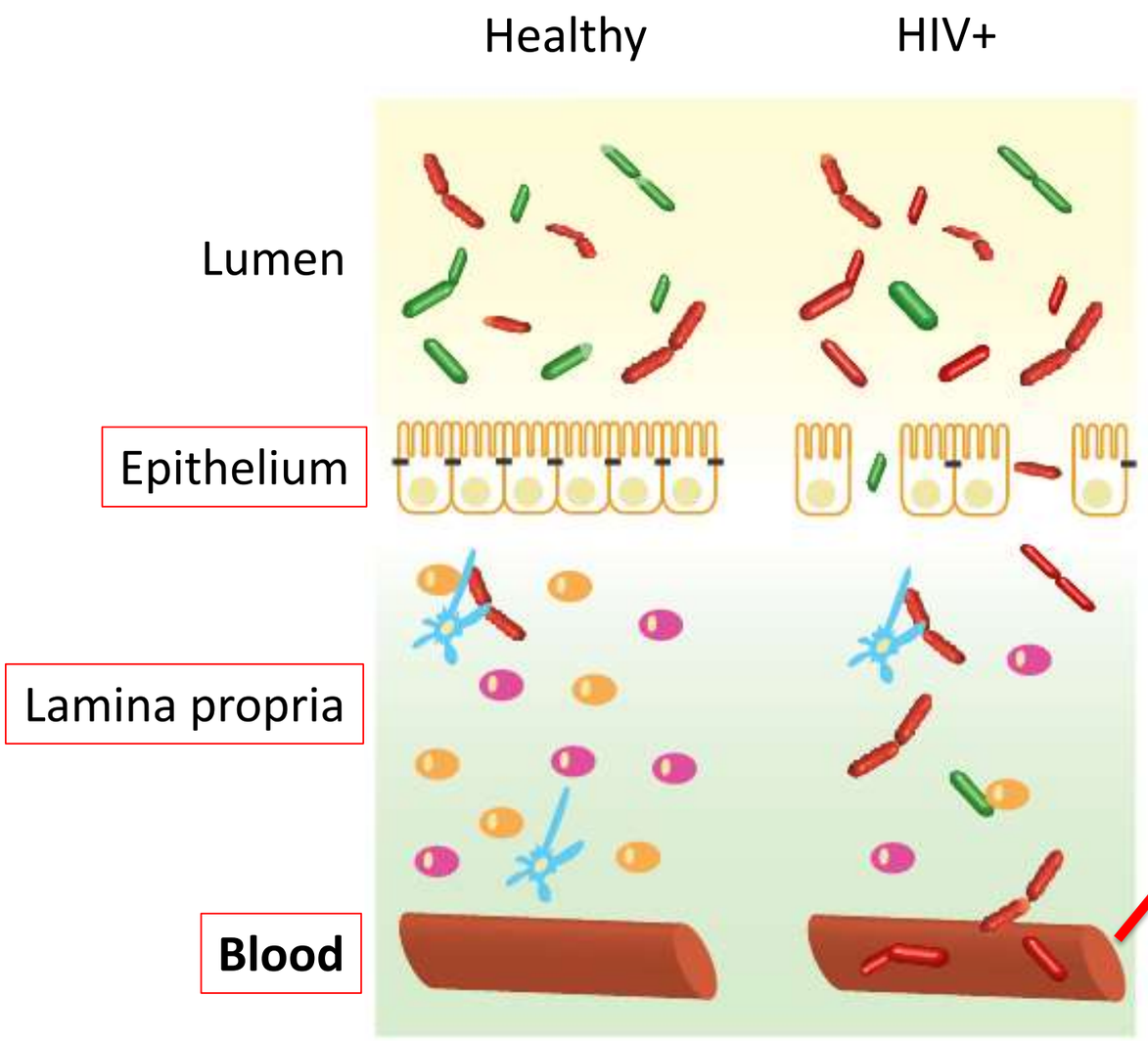
- Increased immune activation (**IL-6, D-dimer**, CRP, CD8 T cell activation) and microbial translocation (LPS) compared to HIV-uninfected people
  (Okulicz, JID 2009; Hunt, JID 2009; Krishnan, JID 2013)

- Increased risk of developing serious non-AIDS conditions that may be driven by inflammation/immune activation
  (Pereyra, AIDS 2012; Okulicz, JID 2009)

Potential factors causing inflammation in EC



Microbial translocation and immune activation



Antiretroviral Therapy?

Microbial translocation

↓

Systemic immune activation

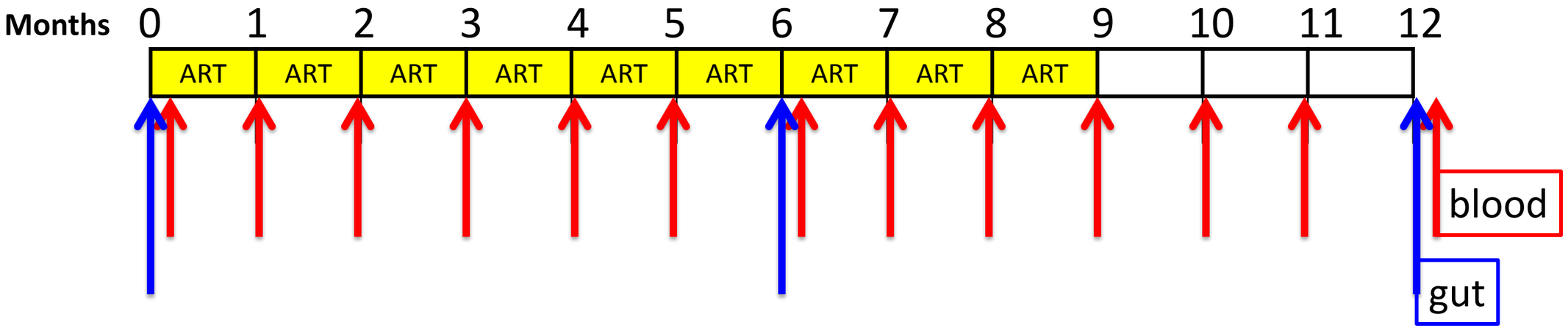
↓

Non-AIDS illnesses, Immune damage

↓

Increased mortality and comorbidities

Study design



- N=4 EC participants
- Sigmoid biopsies for immunology
- Markers of inflammation and microbial translocation
- Viral replication (TW Chun, JID 2013)

Baseline participant characteristics

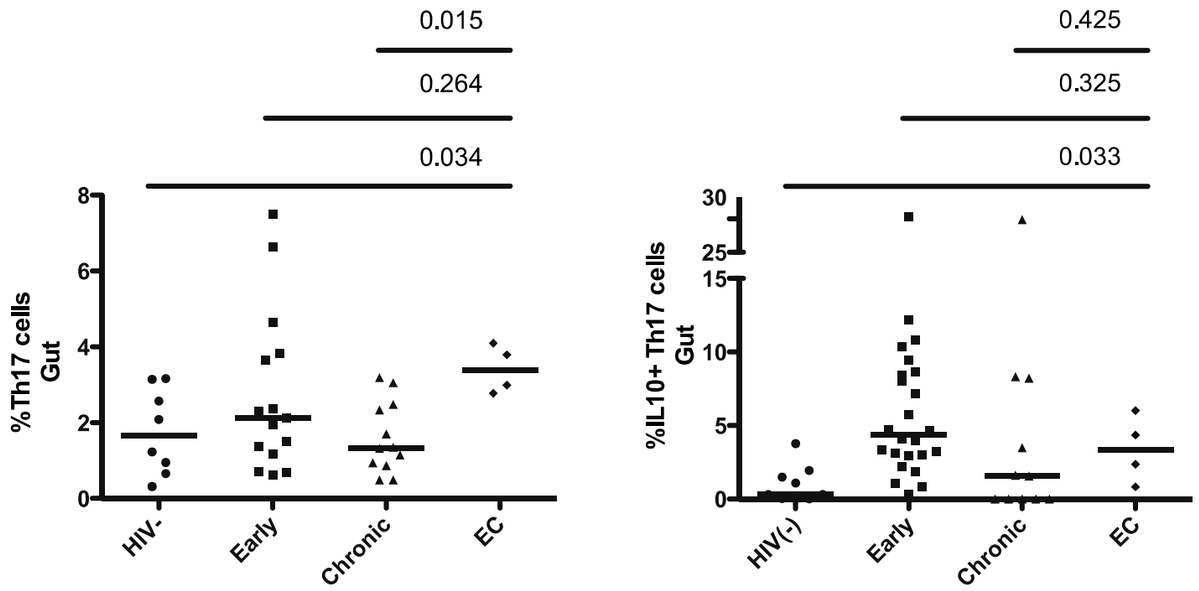
Participant ID	Duration of HIV infection, *years*	Duration of undetectable plasma viremia[1], *years*	Episodes of plasma viremia (highest viral load)[1,2]	Baseline CD4 count, */µl*	Baseline plasma viremia, *c/ml*[3]
A	5	5	0	490	<20
B	23	14	0	550	<20
C	14	9	1 (51)	710	<20
D	23	N/A	8 (372)	660	88

Plasma markers

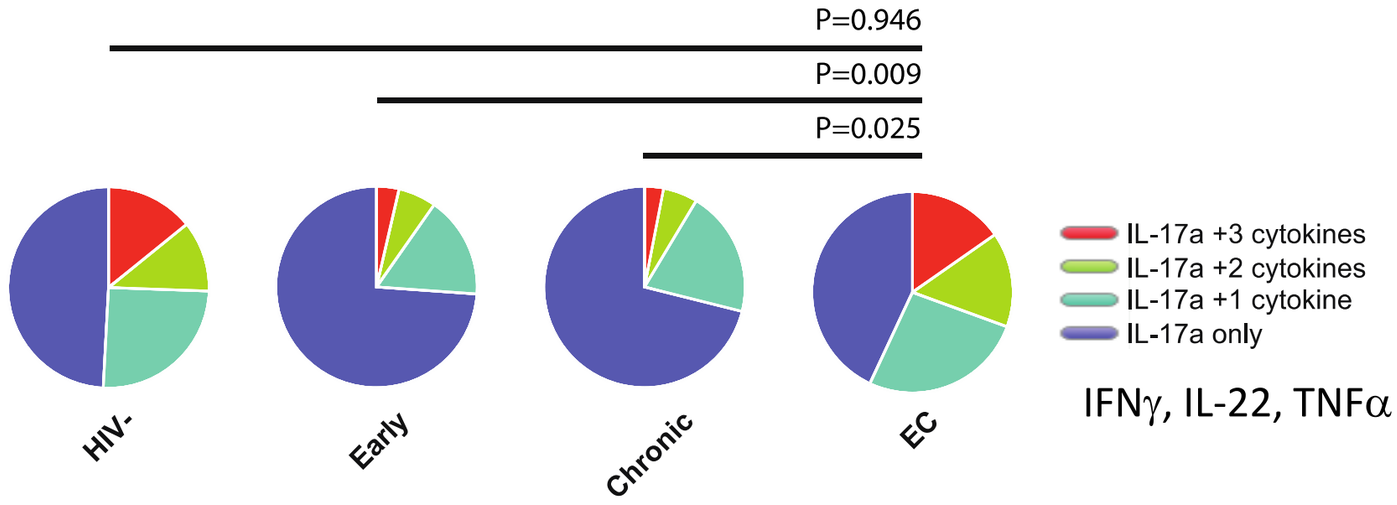
		HIV-	HIV+	EC
Microbial translocation	HLA-DR+CD38+on CD8 T cells,%	2.55 (1.5-6.2) N=7	24.4 (17.9-45.8)* N=10	6.0 (1.6-9.6)# N=4
	LPS, *EU/ml*	1.23 (1.19-1.41) N=8	1.55 (1.36-1.97)* N=12	1.26 (0.89-1.61) N=4
	sCD14, *μg/ml*	1.48 (1.22-1.72) N=8	2.06 (1.82-2.37)* N=12	1.46 (0.94-1.80)# N=4
Coagulatory	D-dimer, *ng/ml*	98.84 (55.42-220.90), N=11	166.2 (55.42-889.4)* N=10	146.3 (115.1-225.8)* N=4
	CRP, *mg/ml*	501.2 (369.4-6104) N=6	1621.0 (348.7-8483) N=6	821.3 (347.5-1245) N=4
Inflammatory	IL-6, *pg/ml*	1.05 (0.62-2.39) N=8	1.86 (0.92-7.56) N=12	1.93 (1.55-5.88)* N=4
	IL-17a, *pg/ml*	1.47 (0.95-2.62) N=8	2.09 (0.82-10.76) N=12	1.28 (0.73-1.51)# N=4
	MIP-1b, *pg/ml*	52.02 (19.63-224.2) N=8	34.22 (24.81-54.28)* N=12	49.66 (30.87-82.51) N=4
	IP-10, *pg/ml*	129.1 (83.36=316.8) N=8	295.5 (154.7-229.2)* N=12	160.3 (50.16-215.1)# N=4
	TNF-α, *pg/ml*	0.92 (0.46-65.37) N=8	1.68 (0.85-5.55)* N=12	0.74 (0.44-1.59)# N=4
Regulatory	IL-10, *pg/ml*	0.65 (0.35-1.40) N=8	1.53 (0.79-3.38)* N=12	0.52 (0.36-0.82)# N=4

*, compared to HIV-; #, compared to HIV+

Gut Th17 cells

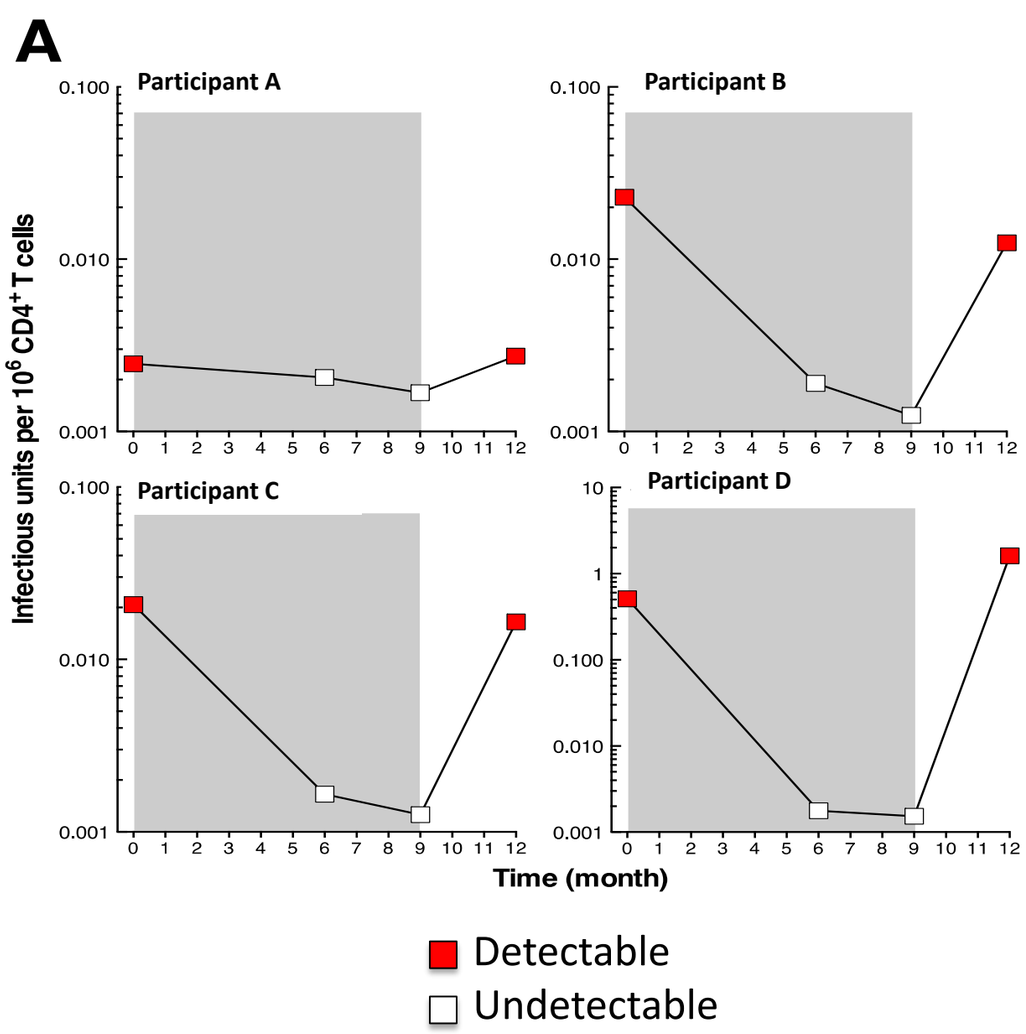


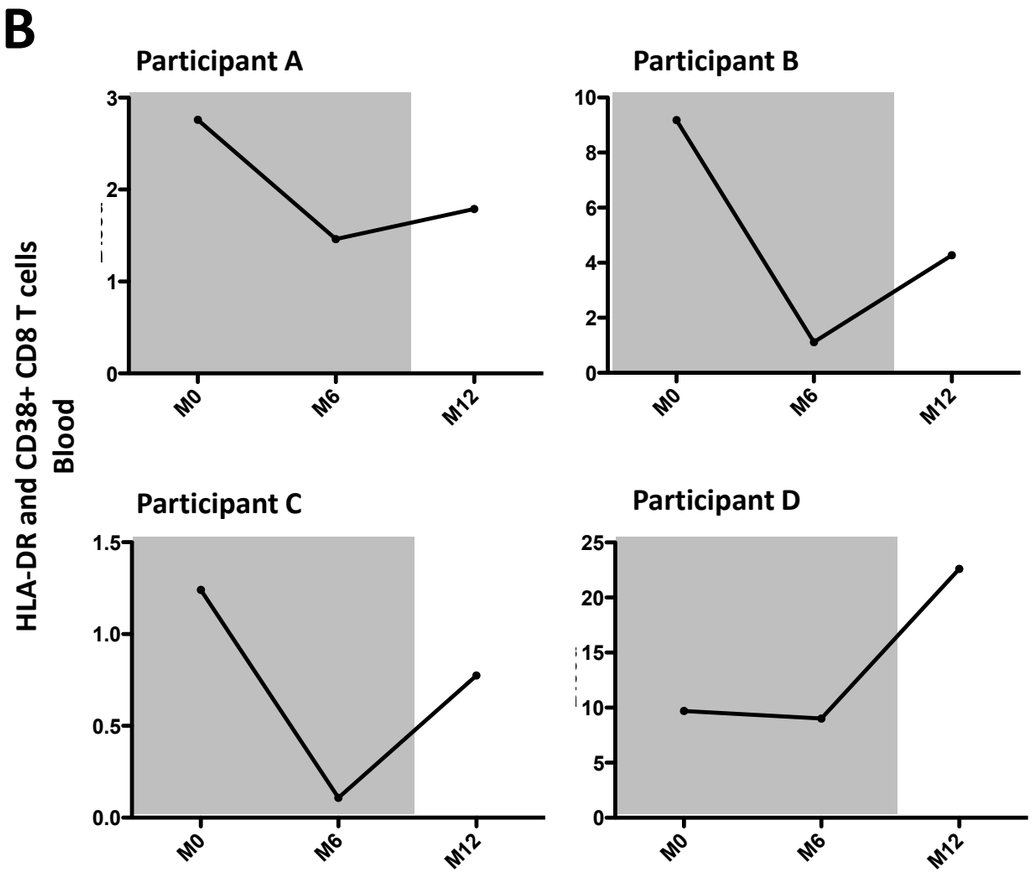
-Normal levels of gut Th1, Th22, Tregs
-Increased frequency of polyfunctional and immunoregulatory gut Th17 cells



IFNγ, IL-22, TNFα

Impact of ART on HIV reservoirs and CD8 immune activation

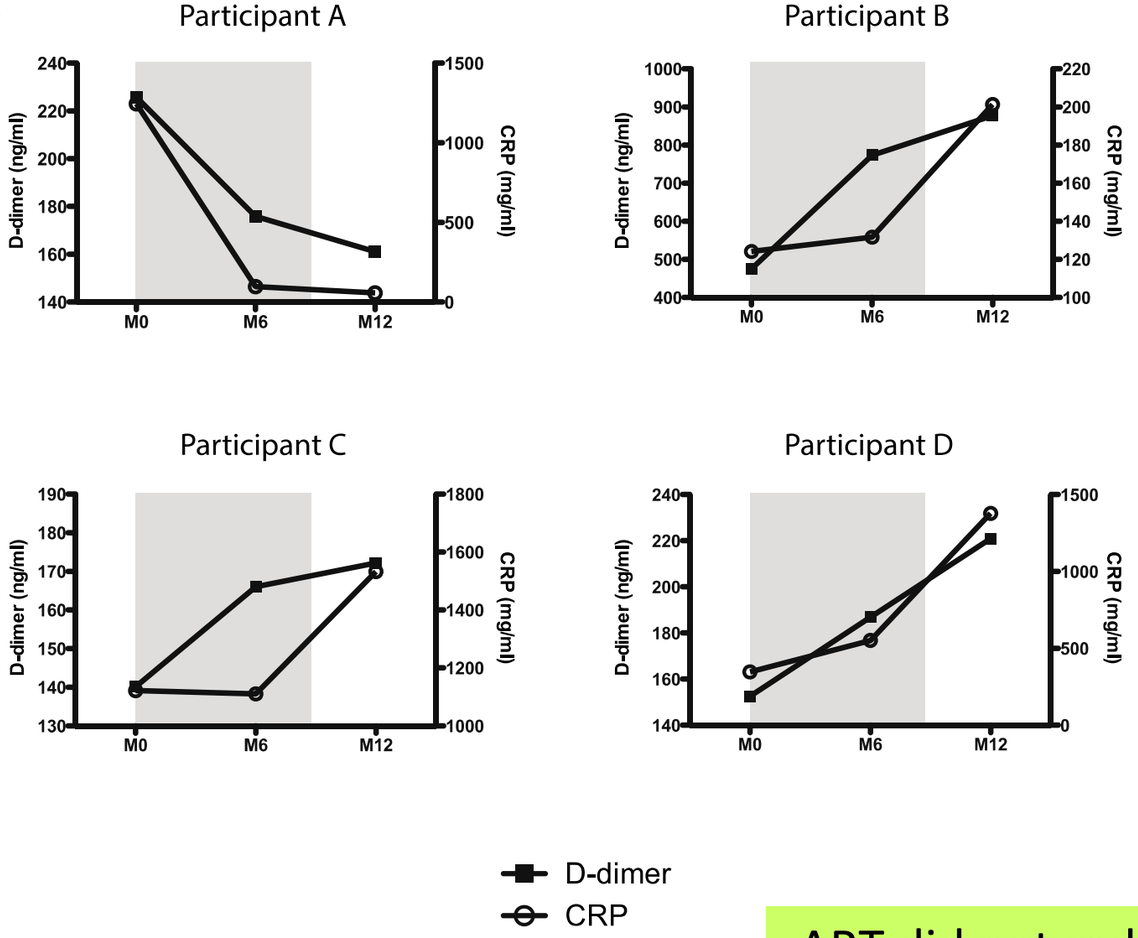




Chun et al, JID 2013

Plasma D-dimer and IL-6 levels after ART

A



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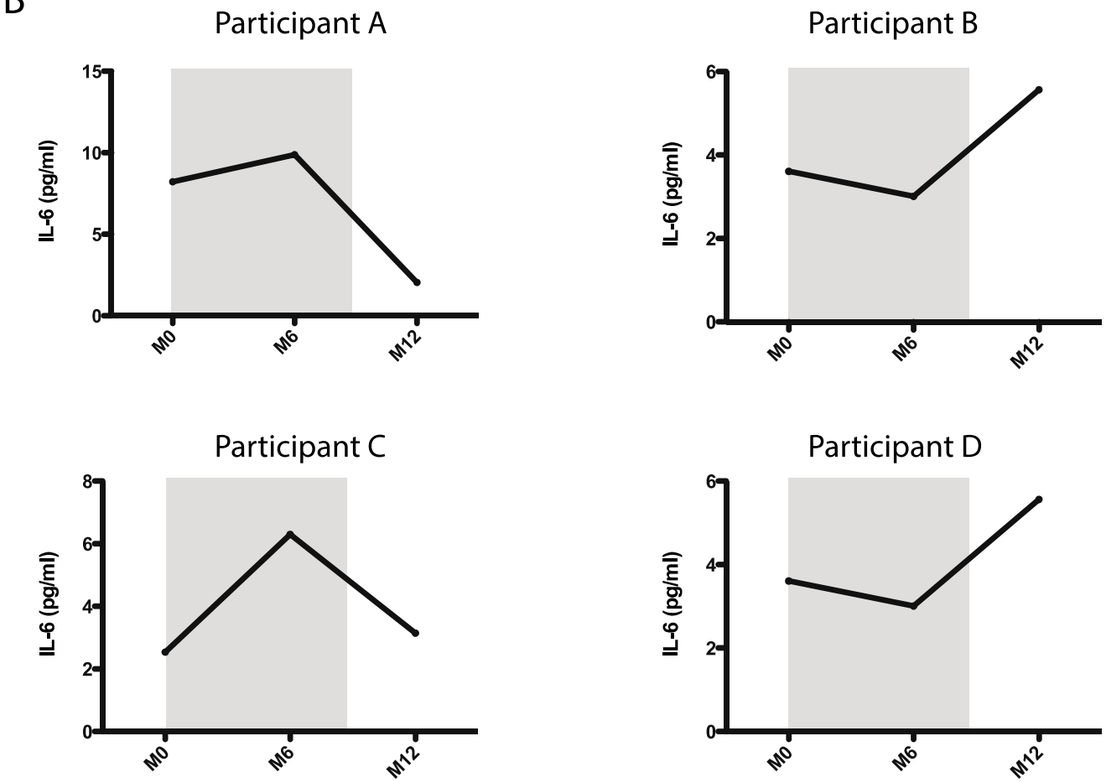

-ART did not reduce IL-6 or D-dimer levels

Conclusions

- EC had normal/enhanced gut immunology and no evidence of microbial translocation; however had elevated levels of IL-6 and D-dimer
  - Implies these can be independent phenomena
- Low levels of viral replication was diminished by ART initiation
- Despite normal gut immunology and diminished viral replication after ART initiation, IL-6 and D-dimer levels were not reduced.

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