Infezione acuta da HIV: patogenesi e implicazioni per il trattamento

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CENTRE FOR MACH
MultidisciplinAry ResearCh in Health Science

Disclosures

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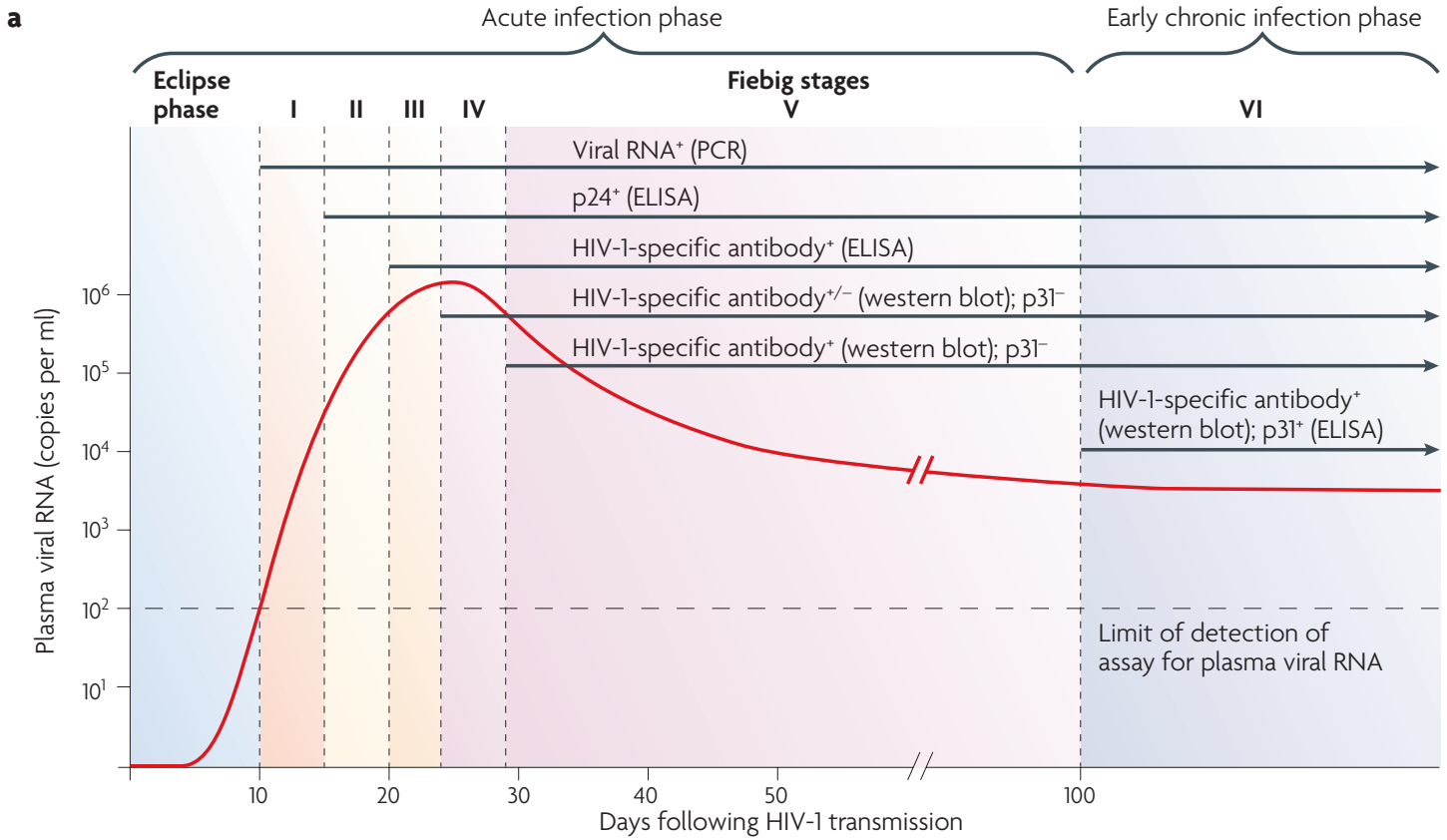
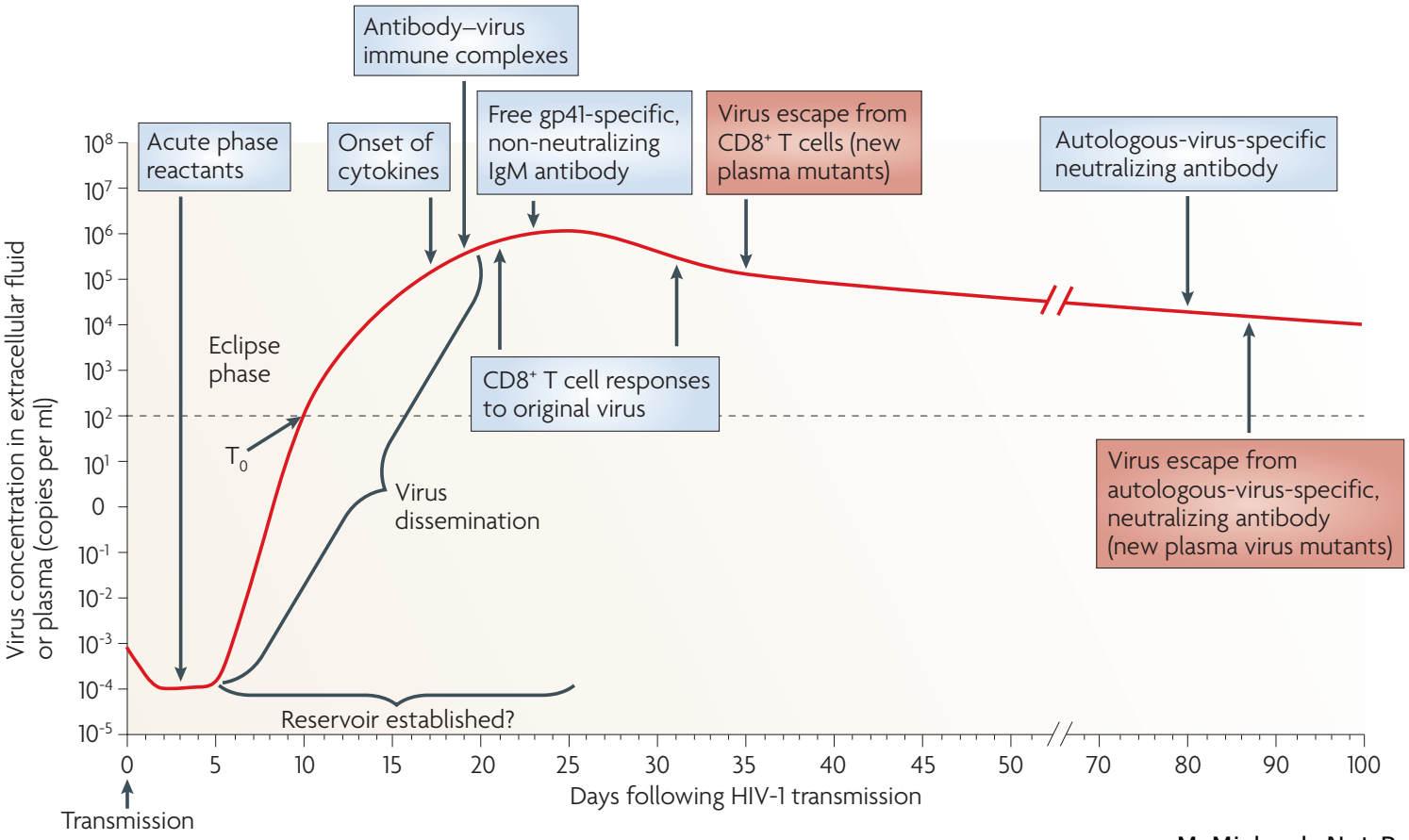
Acute & recent HIV infection



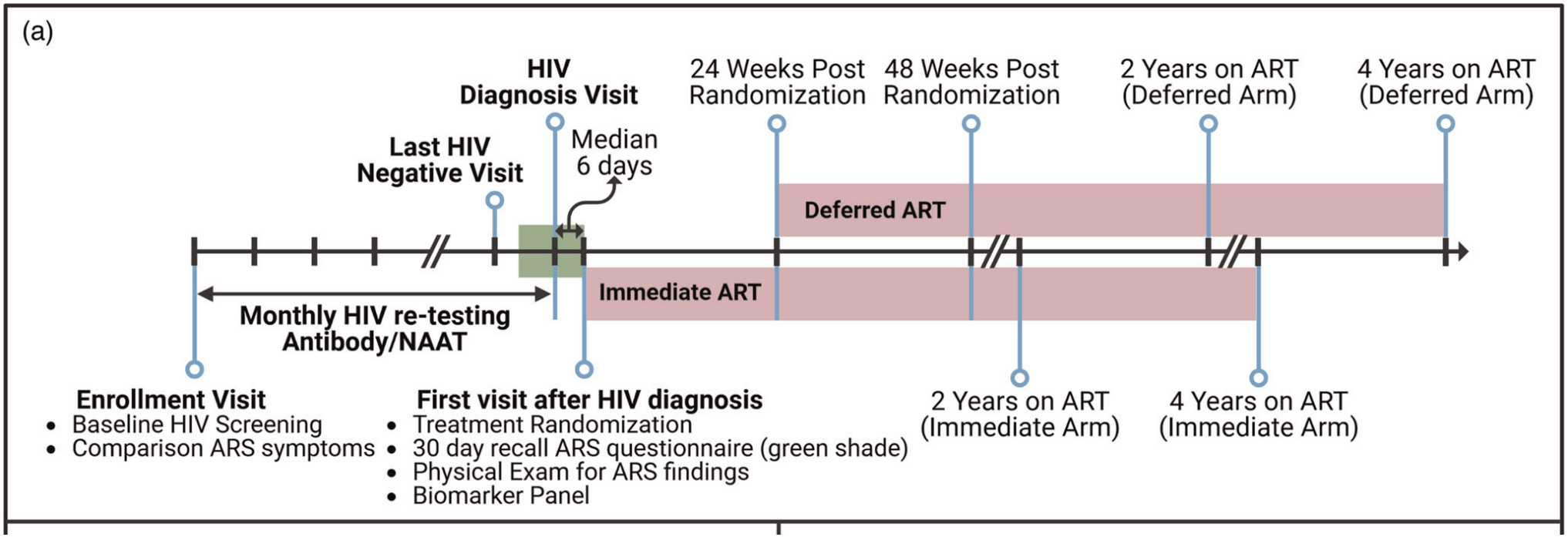
McMichael, Nat Rev Immunology 2010

Acute & recent HIV infection



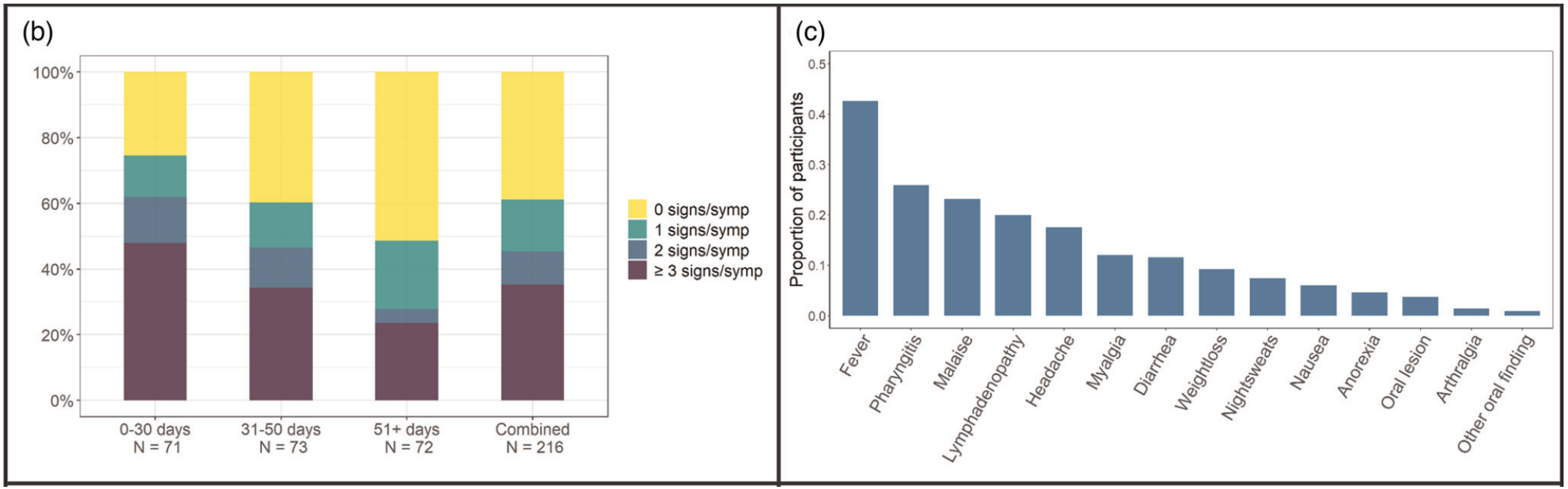
McMichael, Nat Rev Immunology 2010

Sabes study: longitudinal screen, re-test and treat study



Gabert R,et al. AIDS 2023

Sabes study: sign or symptoms of ARS



Gabert R,et al. AIDS 2023

RV217: sign or symptoms of ARS

Fever, headache, and malaise were the most common symptoms

Tachycardia, lymphadenopathy, and other head and neck findings were the most common signs

The greatest number of symptoms was reported at the study visit before the peak viral RNA level (median, 1; range, 0 to 15) and was reported at a median of two visits

Observed signs on physical examination peaked at the visit before the peak viremia (median, 1; range, 0 to 3) and were recorded for a median duration of three visits

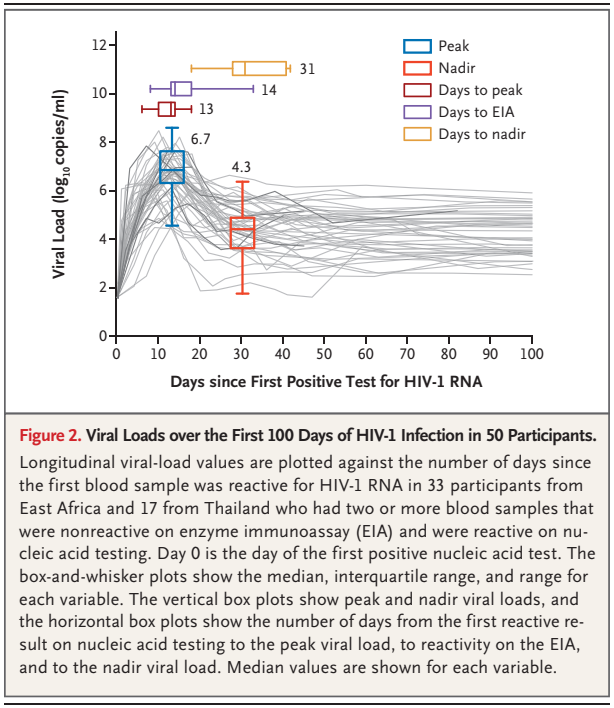


Figure 2. Viral Loads over the First 100 Days of HIV-1 Infection in 50 Participants.
Longitudinal viral-load values are plotted against the number of days since the first blood sample was reactive for HIV-1 RNA in 33 participants from East Africa and 17 from Thailand who had two or more blood samples that were nonreactive on enzyme immunoassay (EIA) and were reactive on nucleic acid testing. Day 0 is the day of the first positive nucleic acid test. The box-and-whisker plots show the median, interquartile range, and range for each variable. The vertical box plots show peak and nadir viral loads, and the horizontal box plots show the number of days from the first reactive result on nucleic acid testing to the peak viral load, to reactivity on the EIA, and to the nadir viral load. Median values are shown for each variable.

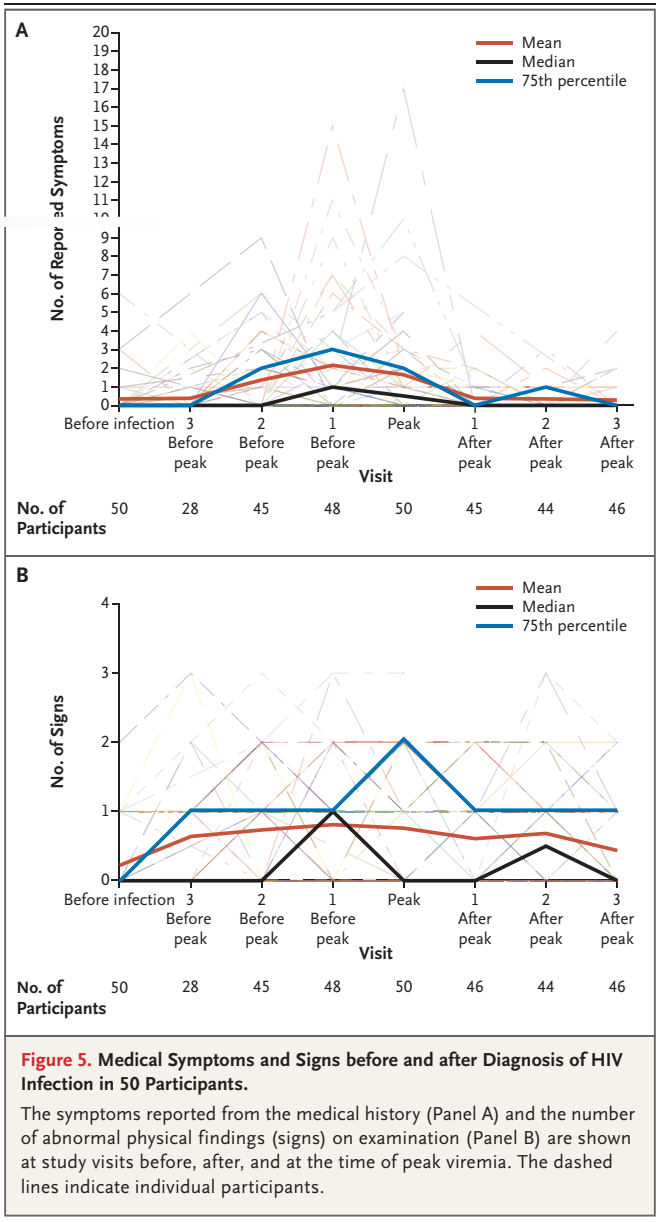
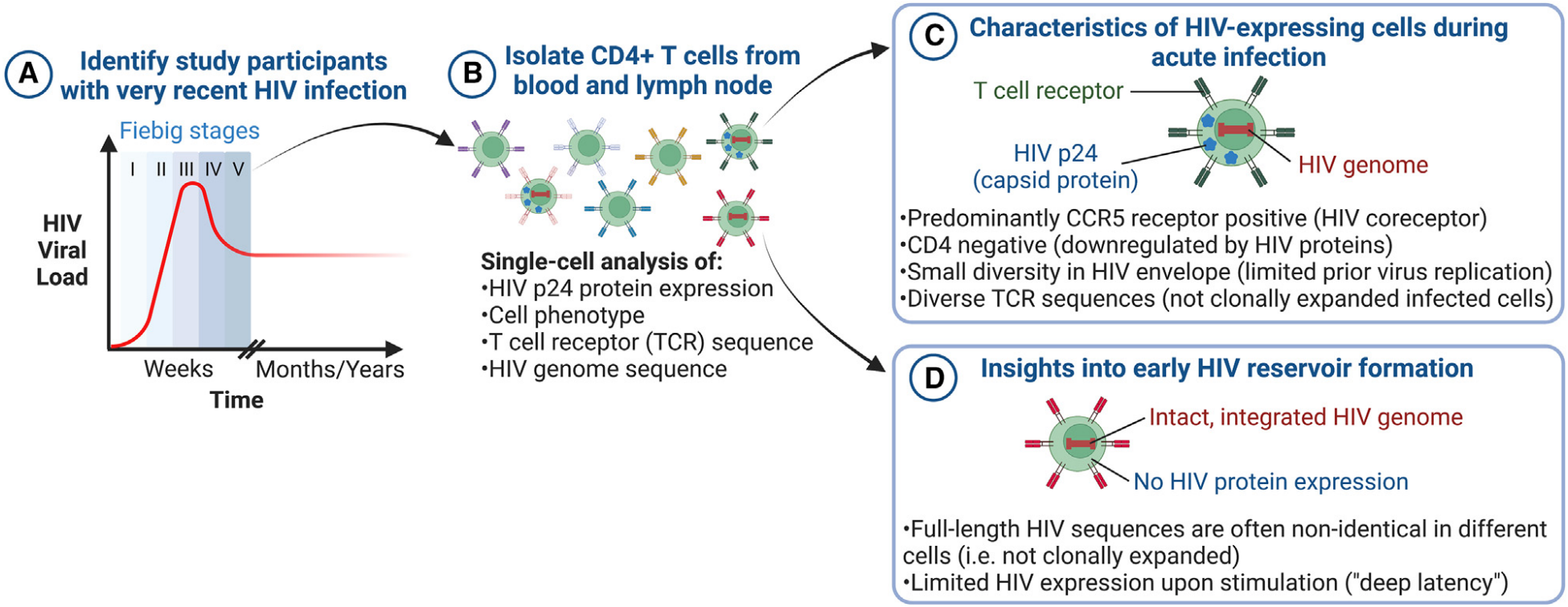


Figure 5. Medical Symptoms and Signs before and after Diagnosis of HIV Infection in 50 Participants.
The symptoms reported from the medical history (Panel A) and the number of abnormal physical findings (signs) on examination (Panel B) are shown at study visits before, after, and at the time of peak viremia. The dashed lines indicate individual participants.

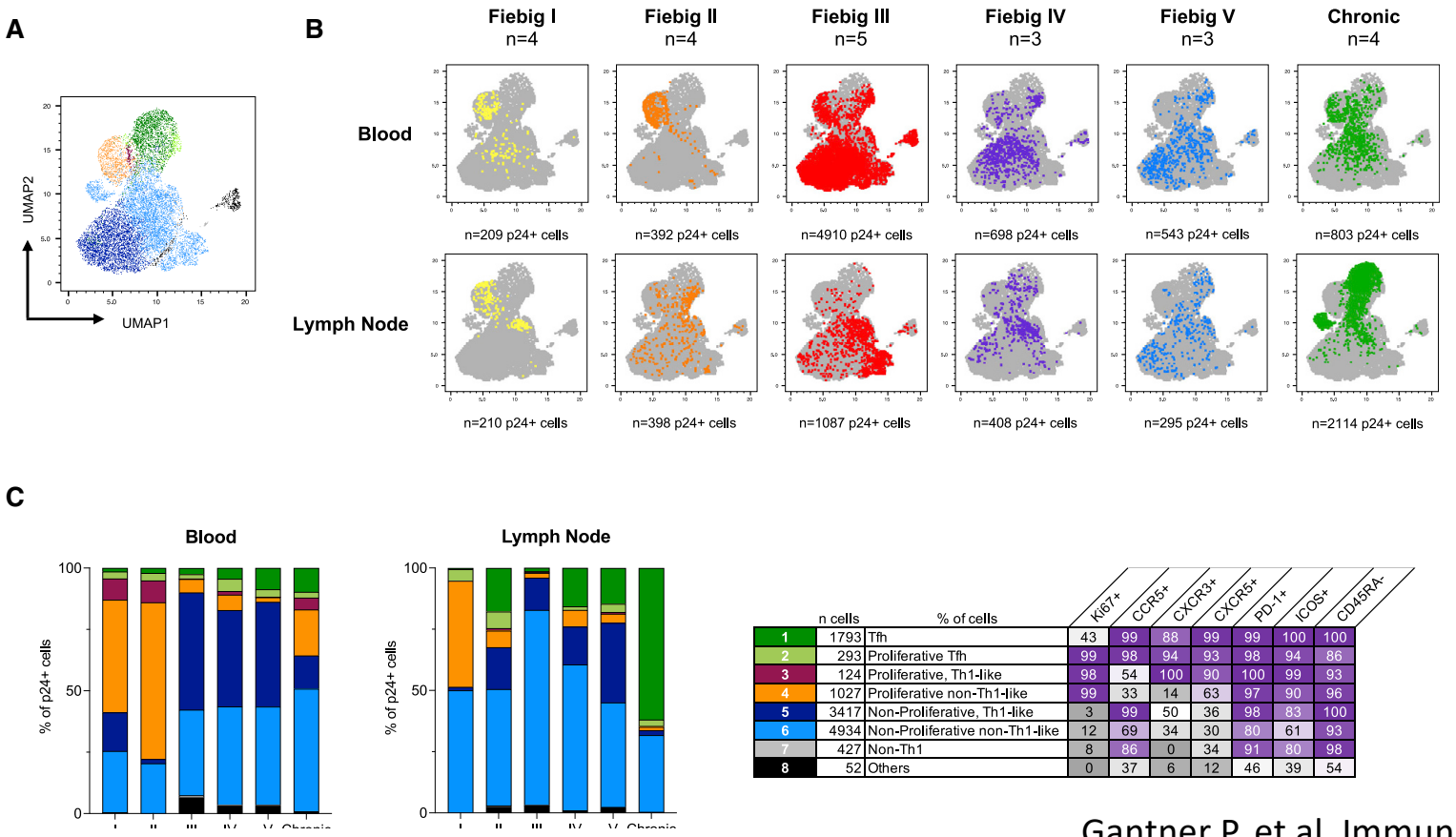
Robb ML,et al. NEJM 2017

HIV establishes an early foothold



Moran JA and Marsden MD. Cell Host Microbe 2023

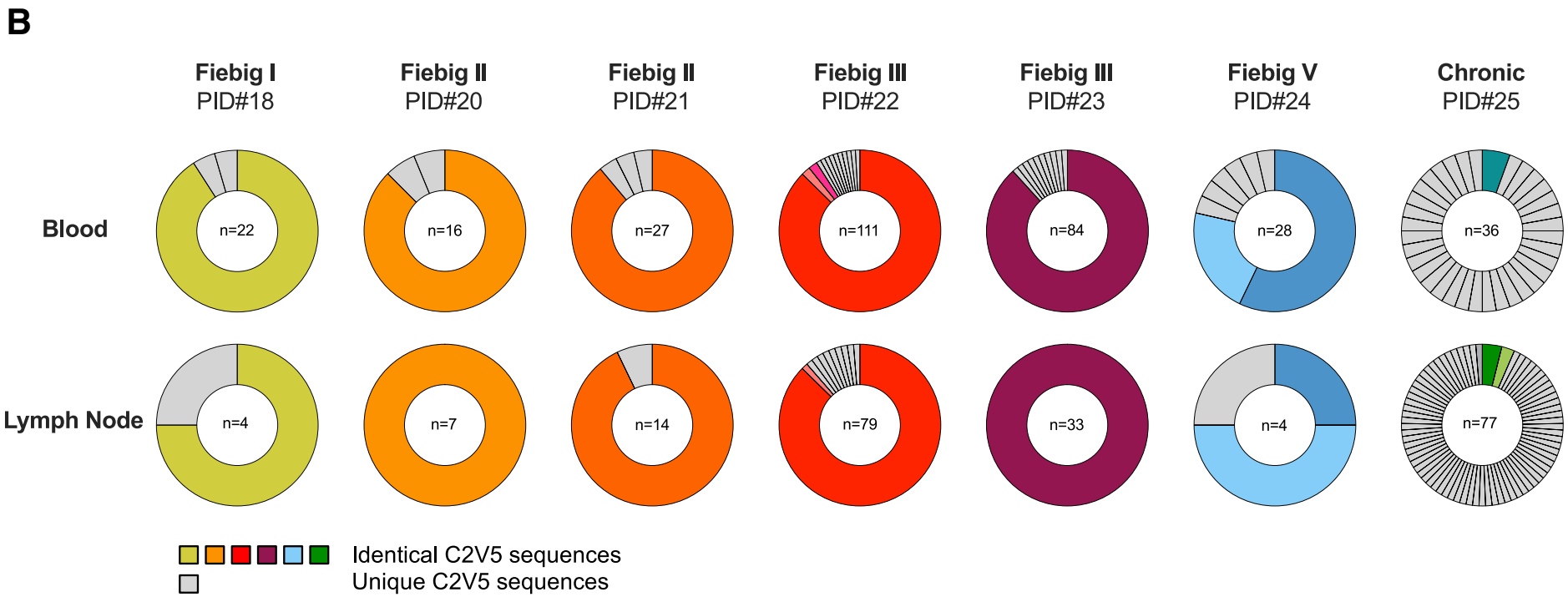
The phenotype of infected cells changes over time and varies between blood and LNs



	n cells	% of cells	Ki67+	CCR5+	CXCR3+	CXCR5+	PD-1+	ICOS+	CD45RA-
1	1793	Tfh	43	99	88	99	99	100	100
2	293	Proliferative Tfh	99	98	94	93	98	94	86
3	124	Proliferative, Th1-like	98	54	100	90	100	99	93
4	1027	Proliferative non-Th1-like	99	33	14	63	97	90	96
5	3417	Non-Proliferative, Th1-like	3	99	50	36	98	83	100
6	4934	Non-Proliferative non-Th1-like	12	69	34	30	80	61	93
7	427	Non-Th1	8	86	0	34	91	80	98
8	52	Others	0	37	6	12	46	39	54

Gantner P, et al. Immunity 2023

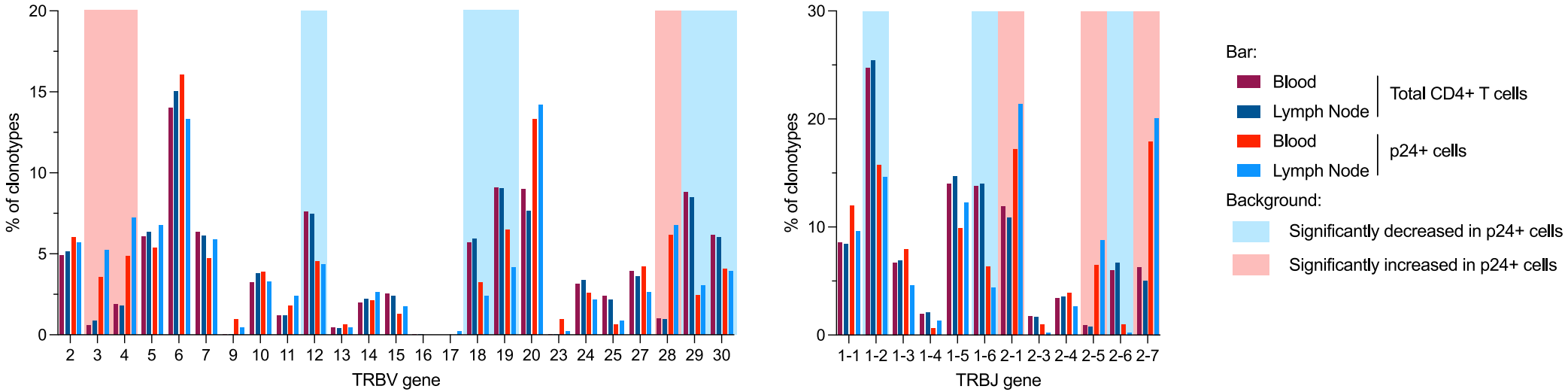
Proviral diversity is limited in productively infected cells during acute infection



Gantner P, et al. Immunity 2023

Productive HIV infection is established in clonotypically distinct T cells from the earliest stages of HIV infection

A



Gantner P, et al. Immunity 2023

CNS viral invasion and inflammation during acute HIV infection

Table 1. Demographic and Clinical Characteristics and Self-Reported History of Risk Factors for 20 Study Subjects With Acute Human Immunodeficiency Virus Infection

Characteristic	Value
Male sex	90%
Age, y, mean (range)	31 (21–46)
Education, y, mean (range)	17 (6–23)
Risk factor	
Male-male sex	85
Injection drug use	0
Heterosexual sex	15
CD4+ cell count, cells/mm^3, median (range)	384 (218–740)
Infection duration, d, median (range)[a]	14.5 (4–31)

Data are no. (%) of subjects, unless otherwise indicated.

[a] Interval between estimated time of exposure and enrollment. If a range of dates was provided, the mean was used.

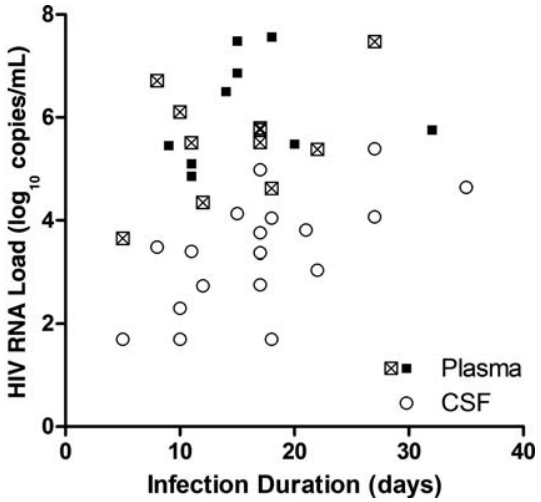


Figure 1. Plasma (squares) and cerebrospinal fluid (CSF; circles) human immunodeficiency virus (HIV) RNA levels, by infection duration. Cases with plasma HIV RNA level measured on the same day as lumbar puncture are represented by open squares, and cases with plasma HIV RNA measured at enrollment are represented by solid squares (median of 2 days before lumbar puncture).

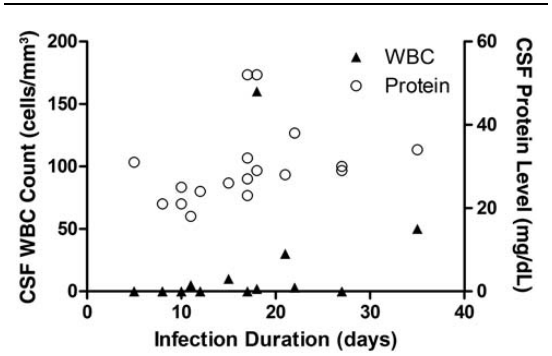


Figure 2. Cerebrospinal fluid (CSF) protein levels (open circles) and white blood cell (WBC) counts (solid triangles) in individuals with acute human immunodeficiency virus infection, by infection duration.

Valcour J,et al. J Infect Dis 2012

CNS viral invasion and inflammation during acute HIV infection

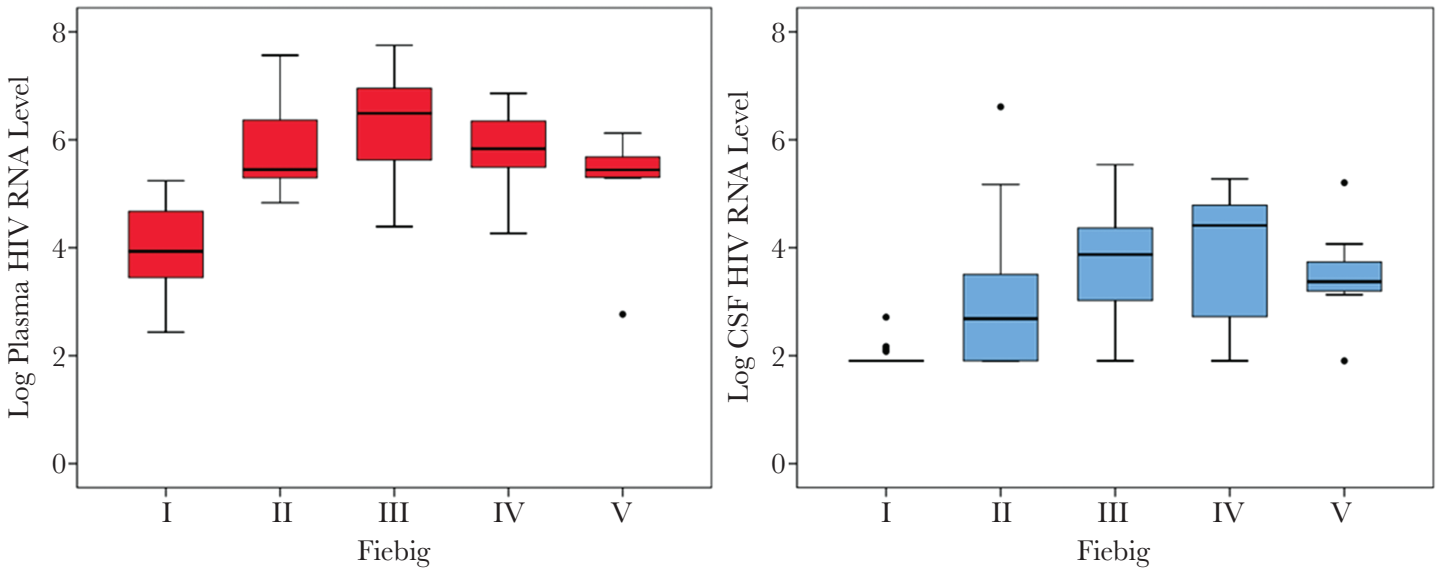


Figure 2. Human immunodeficiency virus (HIV) ribonucleic acid (RNA) level by Fiebig stage (a) plasma and (b) cerebrospinal fluid (CSF). Median (solid line), interquartile range (extent of boxes), 1.5 times of interquartile range (whiskers), and outliers/extreme outliers (stars) are indicated. Number of participants by Fiebig stage (n): I (19); II (24); III (52); IV (15); V (7). A level of 80 copies/mL was assigned to those who had a CSF HIV RNA level below quantification.

Chan P,et al. J Infect Dis 2018

CNS viral invasion and inflammation during acute HIV infection

Table 2. Factors associated with CSF HIV-1 RNA, log10 cps/ml.

	Univariate		Multivariate	
Factors	Coefficient (95% CI)	*P* value	Adjusted coefficient, Beta (95% CI)	*P* value
Age (years)	−0.03 (−0.08 to 0.01)	0.155		
Fiebig stage				
I–II	Ref.			
III–V	1.67 (1.00–2.38)	<0.001		
Acute retroviral syndrome				
No	Ref.			
Yes	2.20 (1.49–2.90)	<0.001		
$CD4^+$ T-cell count (cells/μl)	−0.003 (−0.005 to −0.002)	<0.001	–	
CD8− T-cell count (cells/μl)	0.001 (0.0003–0.0019)	0.007	–	
$CD4^+/CD8^+$ ratio	−2.45 (−3.03 to −1.86)	<0.001	−1.14 (−1.56 to −0.72)	<0.001
Plasma HIV-1 RNA (log_{10} cps/ml)	1.03 (0.86–1.20)	<0.001	0.73 (0.58–0.88)	<0.001
CSF pleocytosis (CSF WBC >5)				
No	Ref.		Ref.	
Yes	1.63 (0.91, 2.35)	<0.001	0.79 (0.41–1.14)	<0.001
CSF glucose (mg/dl)	0.0007 (−0.0026 to 0.0039)	0.682		
CSF protein (mg/dl)	0.01 (−0.03 to 0.06)	0.473		

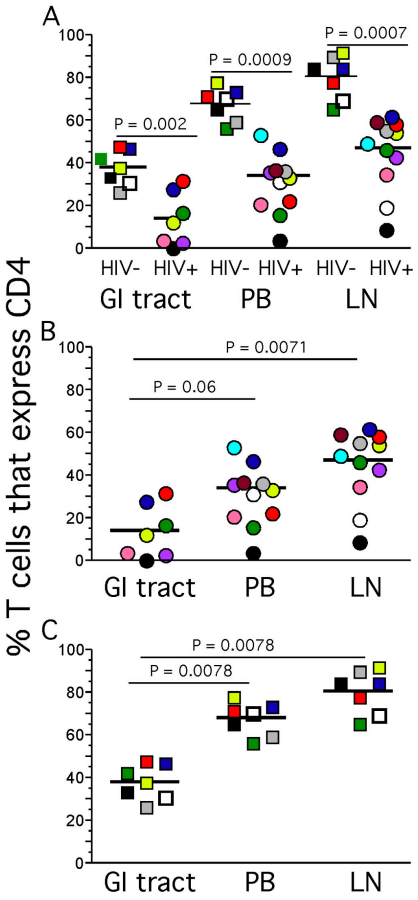
CI, confidence interval; CSF, cerebrospinal fluid; WBC, white blood cell.

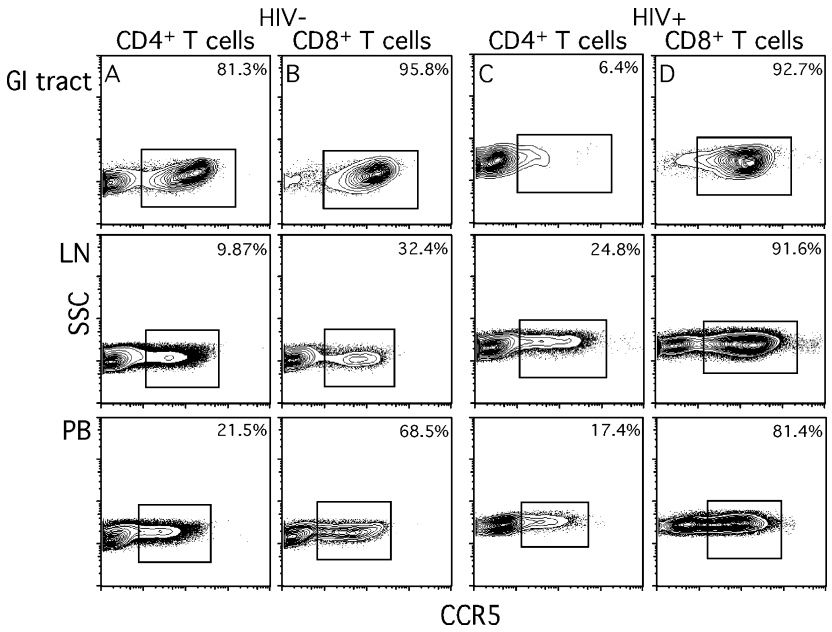
Chan P,et al. AIDS 2024

Depletion of CD4+ cells is particularly dramatic in the GALT

Table I. *Subject Cohort*

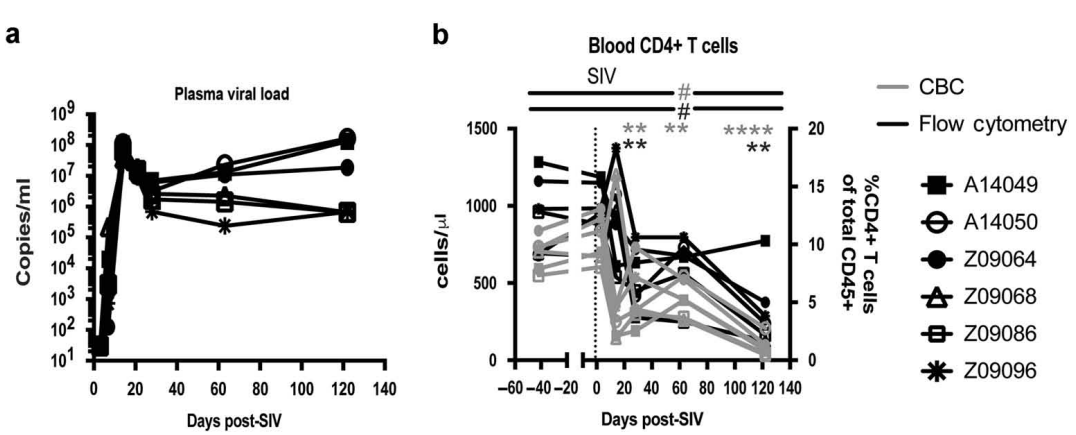
Subject	HIV status	Infection duration	CD4	VL	Collagen deposition
1329	Acute	<1 mo	370	484,694	5.4
1416	Early	4 mo	939	3900	2
1412	Early	9 mo	394	57,329	8
1414	Early	9 mo	491	6465	7.6
1428	Early	8 mo	353	155,207	5.1
1408	Chronic	>5 yr	685	20,014	10
1407	Chronic	>5 yr	372	31,922	2.2
1431	Chronic	>3 yr	333	2,250	5.0
1406	AIDS	>5 yr	188	10,684	19.9
1419	AIDS	8 mo	157	61,432	3.24
1413	AIDS	>5 yr	42	59,401	11.4
1433	AIDS	>2 yr	194	25,000	3.7
1429	LTNP	>5 yr	1,058	2,620	1.9
1415	LTNP	>10 yr	459	129	6.1
1292	HIV⁻	NA	925	0	1.1
1420	HIV⁻	NA	763	0	2.1
1421	HIV⁻	NA	1,497	0	2.6
1423	HIV⁻	NA	675	0	2.3
1424	HIV⁻	NA	734	0	2.5
1425	HIV⁻	NA	1,351	0	0.63
1426	HIV⁻	NA	809	0	0.63



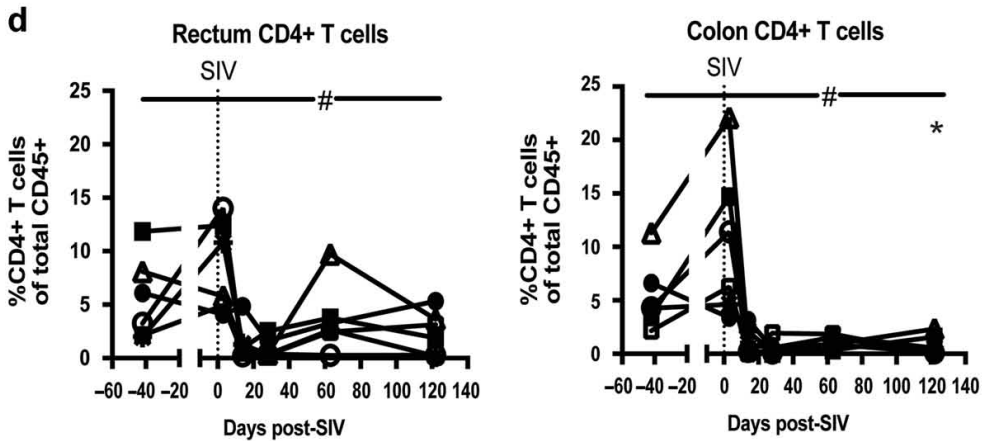


Brenchley, J.M, et al. J Exp Med 2004

Intestinal damage precedes mucosal immune dysfunction in SIV infection



Blood CD4+ T cells declined markedly early in infection and significant depletion was reached 28 days post-SIV.

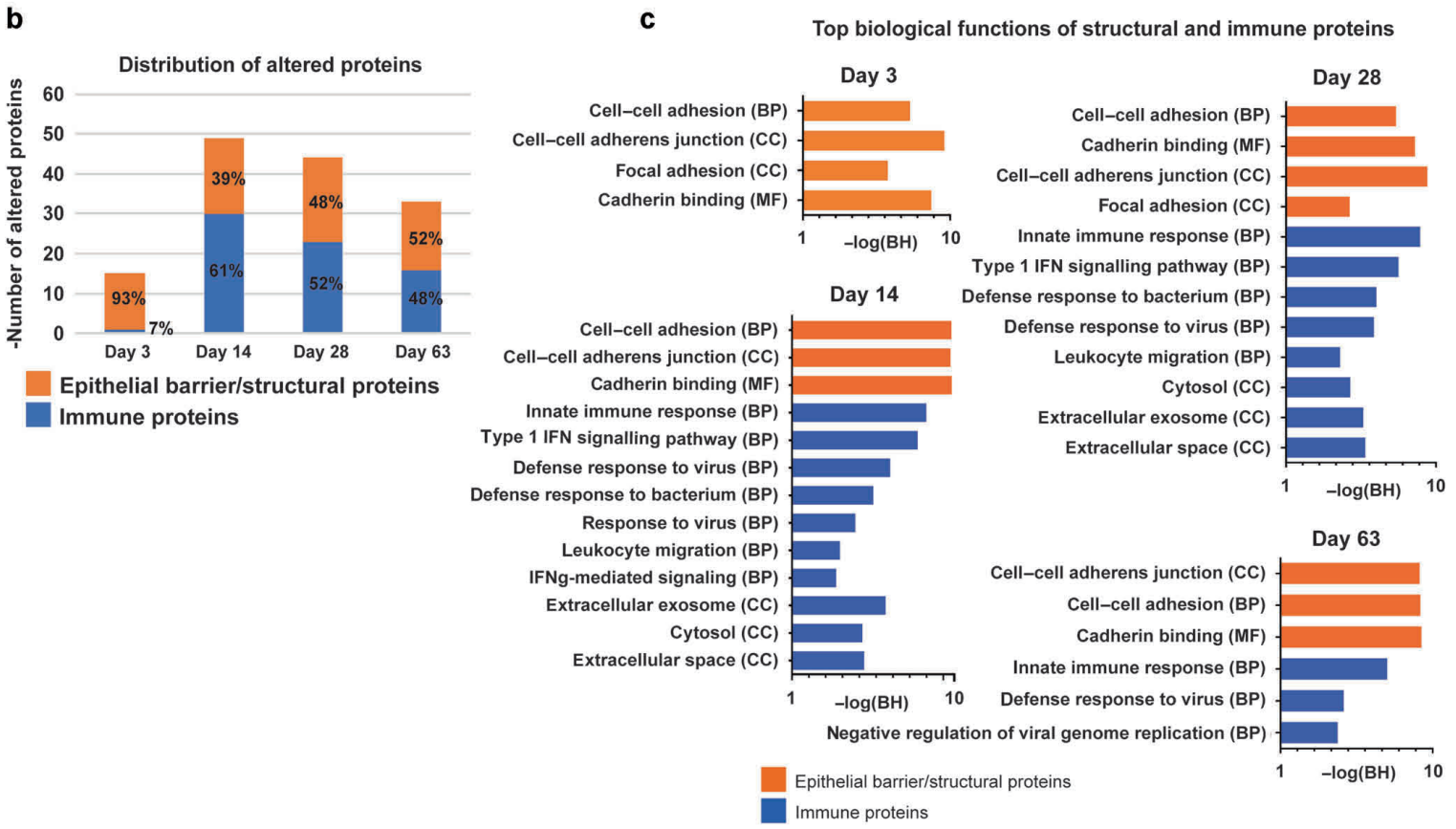


A loss of CD4+ T cells beginning 14 days post-SIV in the colon, although significant depletion was not observed until necropsy

A similar but less dramatic decrease was observed in the rectum

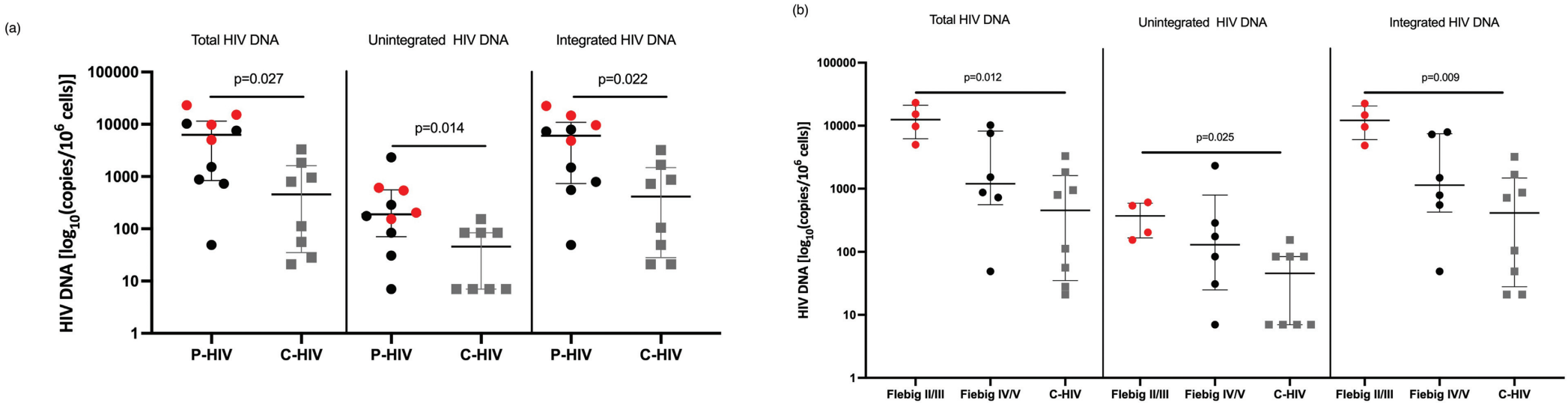
Hensley-McBain T, t al. Mucosal Immunol 2018

Intestinal damage precedes mucosal immune dysfunction in SIV infection



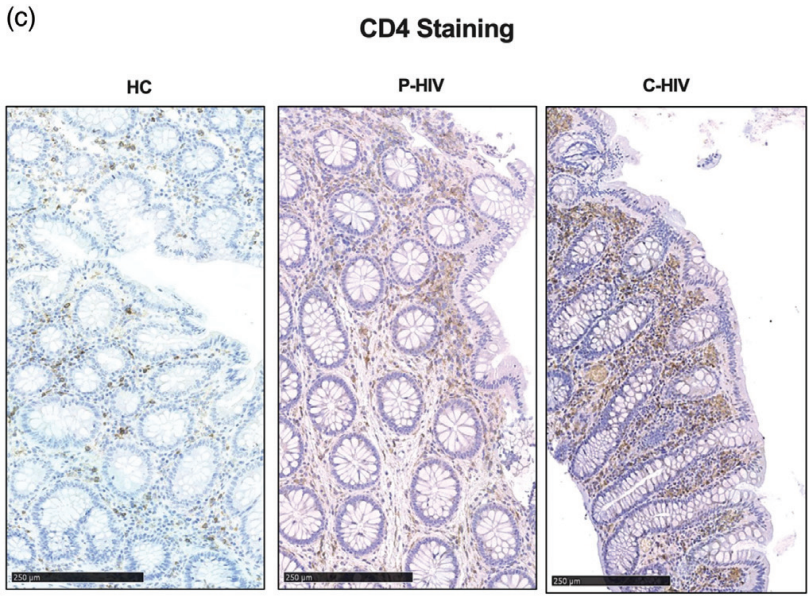
Hensley-McBain T, t al. Mucosal Immunol 2018

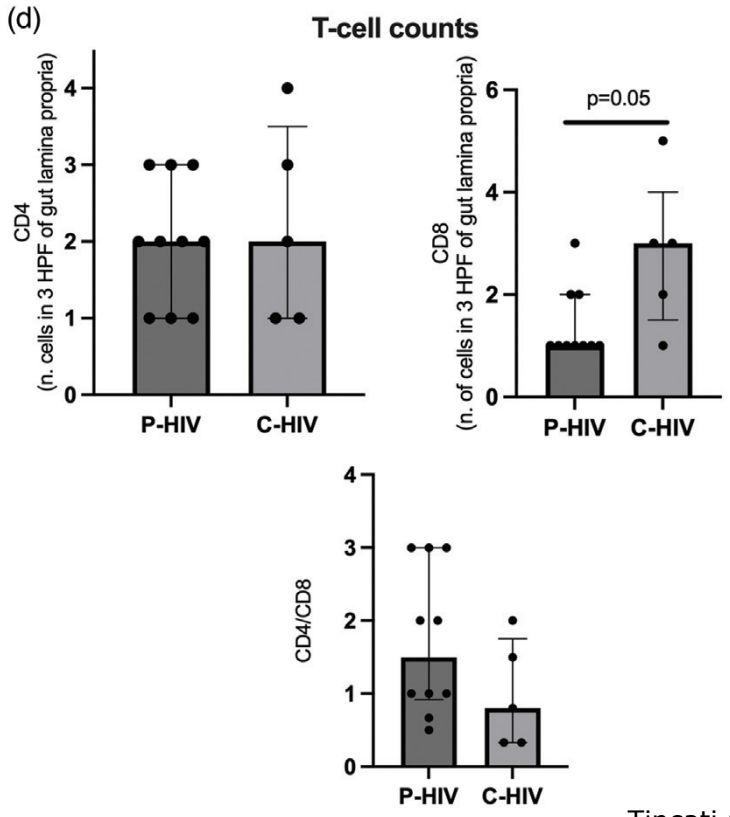
Early HIV infection features higher HIV DNA in the gut



Tincati C, t al. AIDS 2024

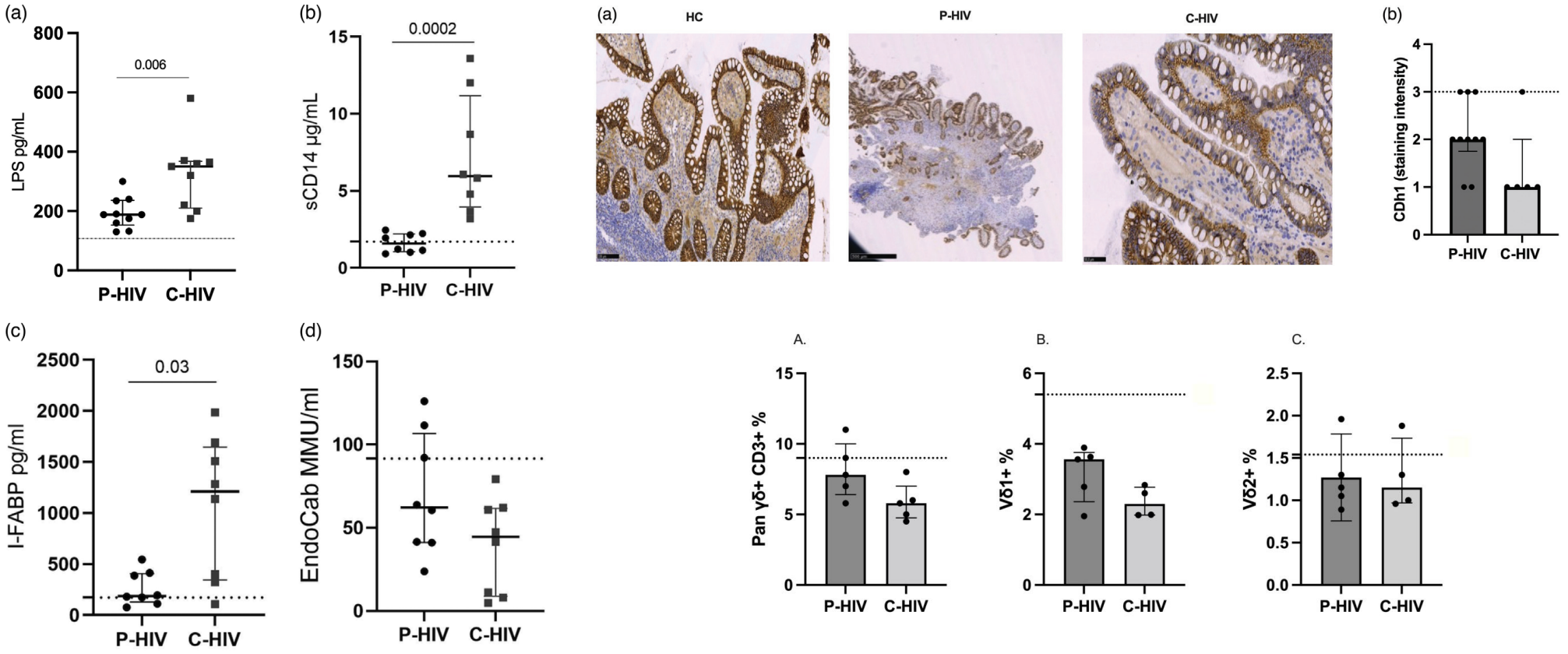
PHI features comparable fibrosis, CD4+ T-cell depletion and neutrophil infiltration in colon biopsies as CHI





Tincati C, t al. AIDS 2024

Microbial translocation is contained during primary HIV infection



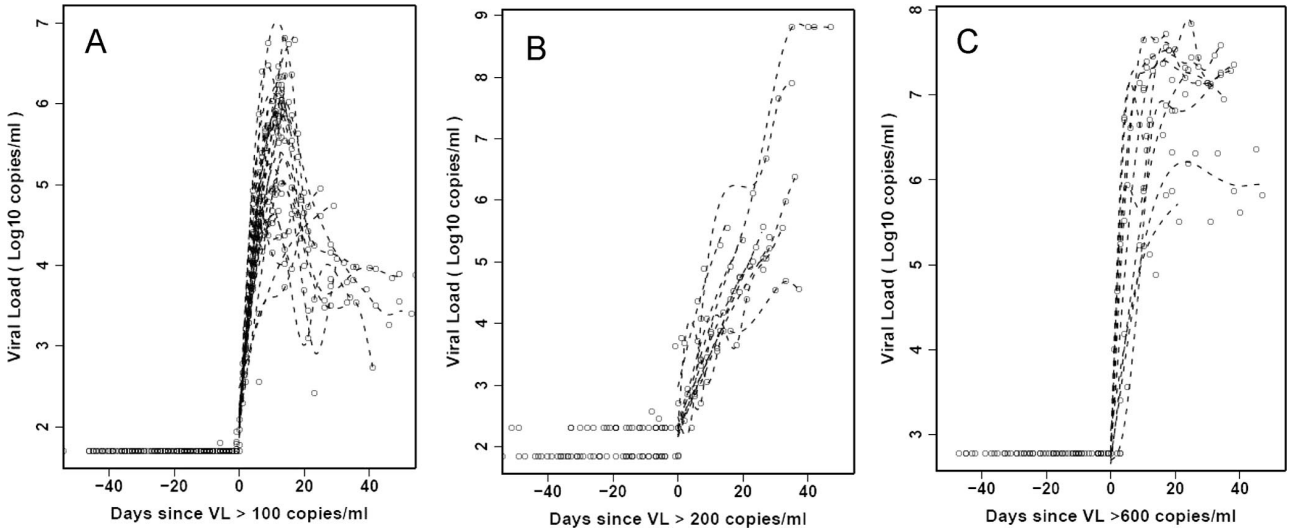
Tincati C, t al. AIDS 2024

Inflammation in acute HIV infection

TABLE 2. Median baseline and highest recorded level of each analyte and median day at which the highest analyte level was recorded in HIV-infected subjects with detectable elevations in levels of analyte

Analyte	Lower limit of assay detection (pg/ml)[a]	Median baseline level (pg/ml)	Median highest recorded level (pg/ml)	Median day of highest recorded level
IP-10	6.5	296.9	2204.9	9
IL-15	0.19	1.9	3.6	6
TNF-α	0.13	3.4	7.7	11.5
IFN-α	12.5	4.6	37.5	7
MCP-1	6.7	59.5	135.3	7
IL-1Rα	1.4	140.4	310.5	9
MIP-1α	2.4	15.2	18.8	10.5
IL-10	0.13	10.3	54.4	12
IL-8	0.13	4.4	11.4	10
IL-17	0.2	3.9	16.6	8.5
IL-6	0.13	4.7	10	12
IFN-γ	0.13	6	17.4	11
Eotaxin	14.60	97.1	149.6	9
IL-18	0.026	196.1	439.3	11.5
MIP-1b	1.1	66.5	92.2	9
VEGF	0.5	11.7	27.4	16
IL-4	0.13	10.1	22.6	15.5
FGF basic	6.8	72.8	108.7	10.5
G-CSF	1.1	59.6	71.2	13
IL-22	15.6	14.1	29	12
GM-CSF	0.13	2.3	4.8	18
IL-7	0.13	2.3	4.6	13
IL-9	0.7	84.3	129.4	14
IL-12(p70)	0.13	2.3	5.3	13.5
IL-2	0.13	2.2	9.2	16
IL-5	0.13	0.7	1.4	16
IL-13	0.13	2.9	14.9	18
IL-1β	0.13	0.6	2.3	16
PDGF-BB	1.00	636.6	1,395.2	14
RANTES	1.2	5,966.3	9,849.4	16

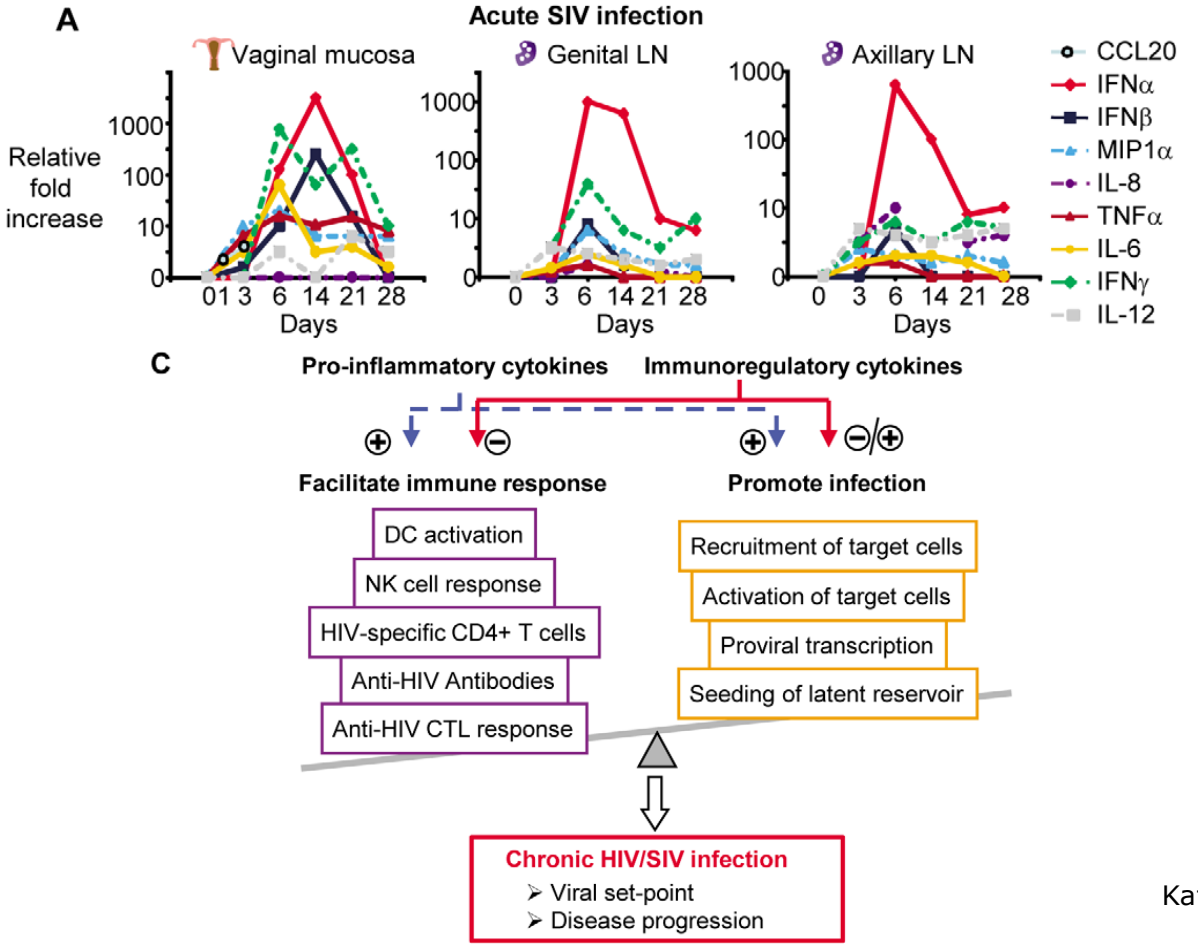
[a] Lower limit of analyte detection in Luminex assays as determined by the assay manufacturer or bottom point on the standard curve for analytes measured by ELISA.



The increase in plasma viremia in acute HIV-1 infection was found to be associated with elevations in IFN-alpha and IL-15 levels; a large increase in IP-10 levels; rapid and more sustained increases in TNF-alpha and MCP-1 levels; more slowly initiated elevations in levels of additional proinflammatory factors including IL-6, IL-8, IL-18, and IFN-g; and a late peaking increase in levels of the immunoregulatory cytokine IL-10.

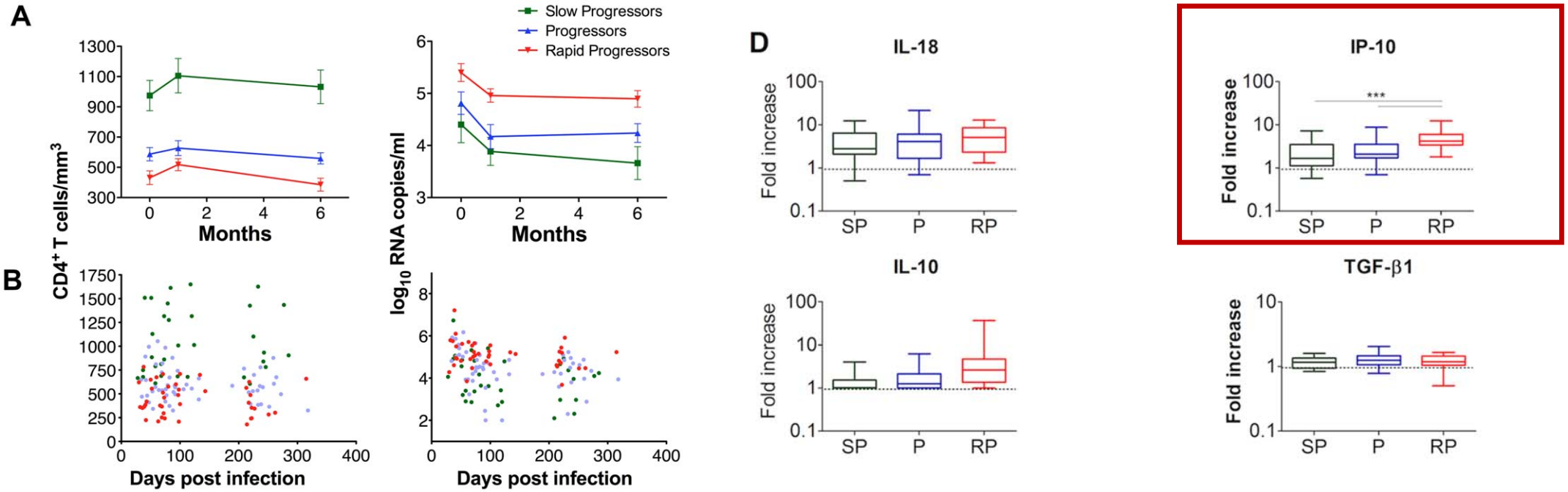
Stacey JR J Virol 2009

Inflammation in acute pathogenic and non-pathogenic SIV infection



Katsikis PD PlosOne 2011

Effect of inflammation on HIV progression



In acute infection, high IFNg-induced protein 10 (IP-10) levels predicted disease progression, defined as CD4 T-cell loss

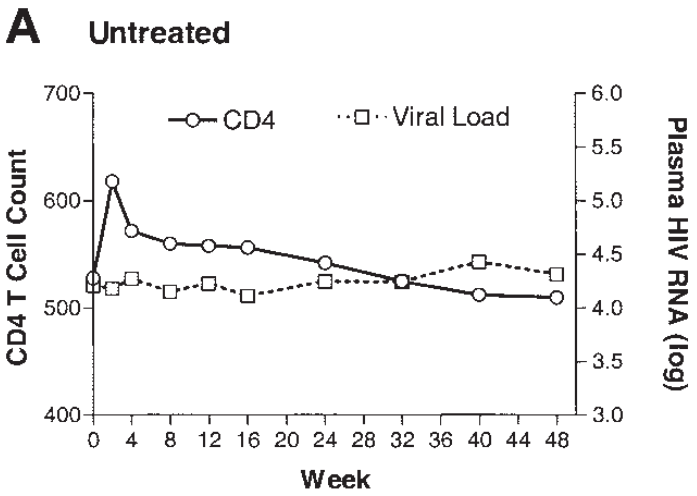
Liovat AS PlosOne 2012

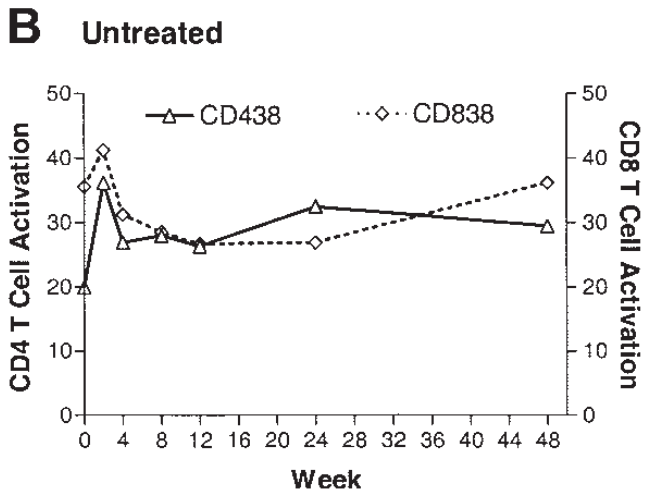
Lymphocyte activation during AHI

Table 1. Baseline characteristics

Characteristics	Treated, n = 83	Untreated, n = 68	*P*
Age, y (IQR)	35 (30-40)	34 (30-41)	.97
Sex, %	94	96	.73
Infection stage, %			.001
Less than 30 d	24.1	2.9	
1 to 6 mo	71.1	88.2	
6 to 12 mo	4.8	8.8	
Presence of one or more drug-resistance associated mutations, %	17.4	17.8	1.0
HIV risk factors, %			
MSM	94.0	100	.07
Intravenous drug user	4.4	2.4	1.0
$CD4^+$ T-cell count, cells/mm^3 (IQR)	484 (374-646)	539 (451-717)	.03
$CD8^+$ T-cell count, cells/mm^3 (IQR)	798 (572-1071)	817 (632-1086)	.68
Plasma HIV RNA level, log_{10} copies RNA/mL	5.10 (4.18-5.63)	4.26 (3.36-4.70)	< .0001
Baseline $CD4^+$ CD38, relative fluorescence units	33.2 (23.3-46.4)	19.7 (8.2-41.4)	.004
Baseline $CD8^+$ CD38, relative fluorescence units	99.6 (39.6-256)	33.4 (9.8-67.6)	< .0001

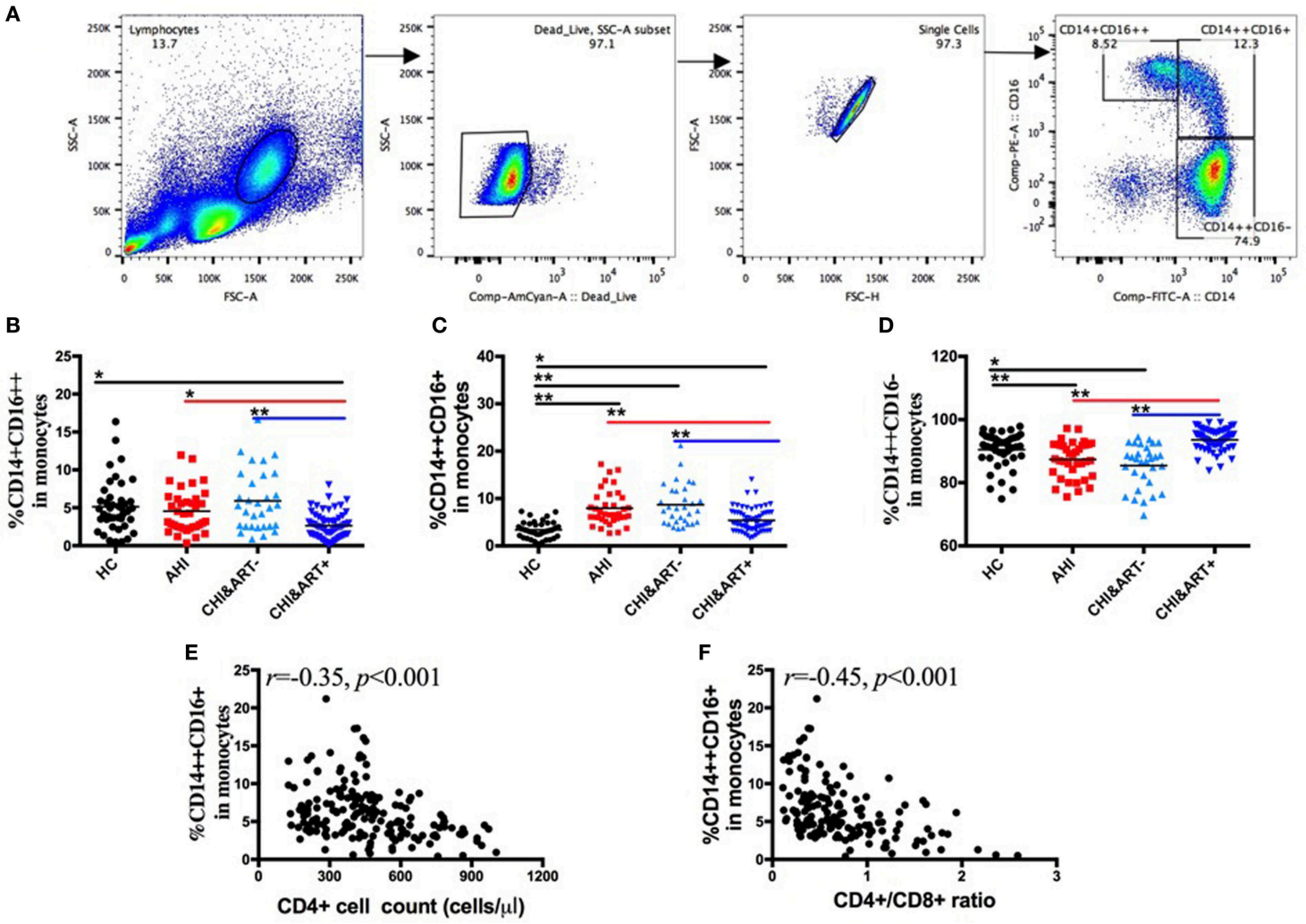
Median and interquartile ranges (IQRs) are shown. MSM indicates men who have sex with men.





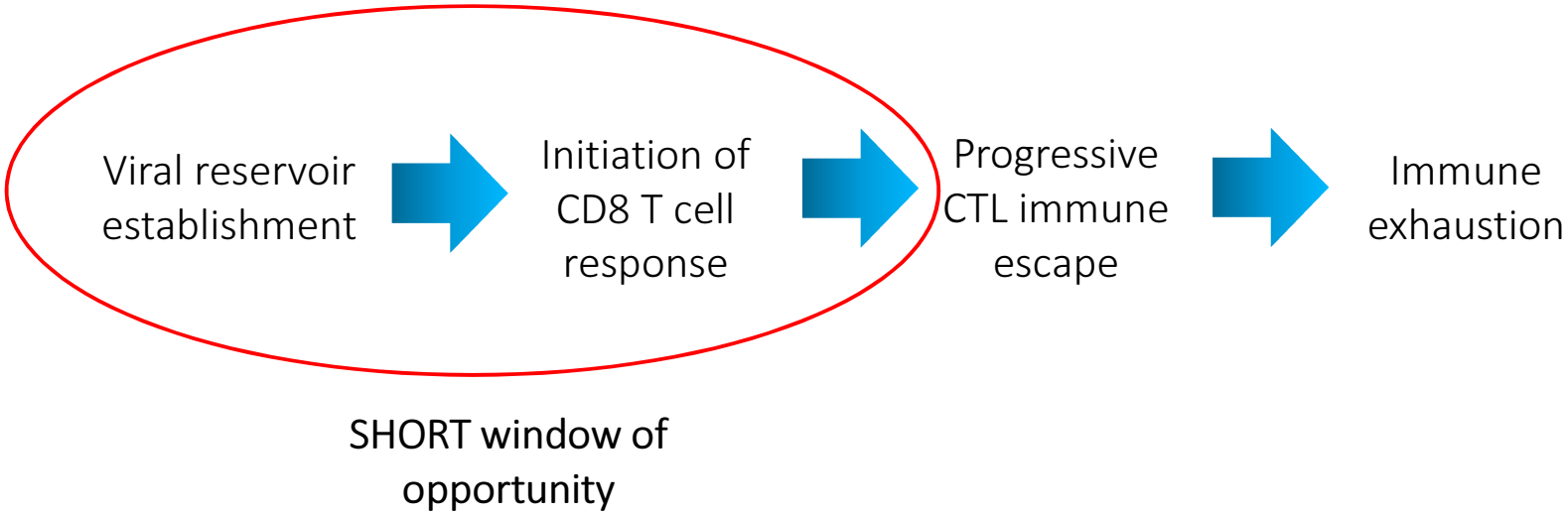
Deeks SG Blood 2014

Monocyte perturbation during AHI



Cheng P Front Immunol 2017

Acute & recent HIV infection

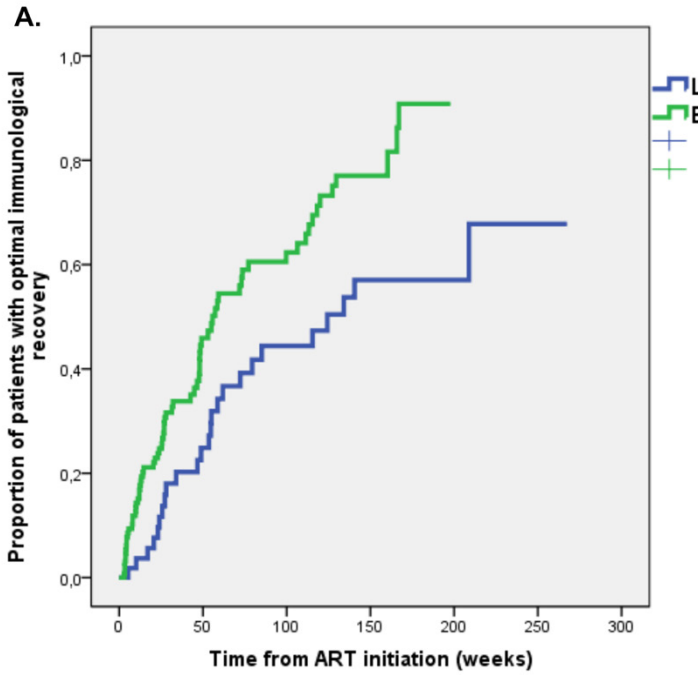


Courtesy of Beatriz Mothe

ART initiation during acute HIV infection

- Decrease in duration/severity symptoms
- Enhances recovery of CD4 cell populations
- Decrease viral transmission (10-20x infectious in acute stage)
- Limit (not prevent) viral reservoir seeding and frequency of VL blip
- Reduce CTL escape
- Preserve immune function → better vaccine responsiveness?
- Higher chances to become PTC once ART is interrupted

Enhanced immunological recovery with early start of antiretroviral therapy during acute or early HIV infection: INACTION Retrospective Study



Predictors of time to optimal immunological recovery (n=187)	Univariate analysis		Multivariate analysis	
Early ART	2.076 (1.297-3.323)	**0.002**	1.846 (1.041-3.273)	**0.036**
First ART regimen including:				
NNRTI	0.827 (0.511-1.338)	0.440		
PI	1.017 (0.649-1.593)	0.941		
InSTI	1.960 (1.196-3.214)	0.008		
Entry inhibitor	1.369 (0.775-2.417)	0.279		
First ART regimen >3 drugs	1.936 (1.230-3.048)	**0.004**	1.413 (0.844- 2.366)	0.188
Laboratory results at first ART initiation:				
CD4, cells/mm3 (per 100cell/mm3 increase)	1.149 (1.061-1.243)	**0.001**	1.119 (1.018-1.229)	**0.020**
CD4% (per 1% increase)	1.064 (1.040-1.089)	**<0.001**	1.042 (1.014-1.070)	**0.003**
CD8, cells/mm3 (per 100cell/mm3 increase)	0.981 (0.962-1.000)	0.053		
CD4/CD8 >1	4.152 (2.005-8.599)	**<0.001**	2.839 (1.165-6.914)	**0.022**
HIV-RNA, log10cps/mL (per 1log10cp/mL increase)	1.149 (0.918-1.437)	0.225		
Year of diagnosis, 2012-2014 vs. 2008-2011	1.242 (1.081-1.427)	**0.002**	1.555 (0.902-2.681)	0.112

Muscatello A, et al Pathog Immun 2020

Predictors of incomplete viral response in patients with acute and early HIV infection: INACTION Retrospective Study

	Univariate analysis HR (95% CI)	P	Multivariate analysis aHR (95% CI)	P
CNS symptoms				
No	Ref		Ref	
Yes	3.06 (1.07-8.72)	**0.036**	4.70 (1.56-14.17)	**0.006**
Unknown	2.05 (0.79-5.30)	0.139	2.44 (0.90-6.61)	0.080
Backbone:				
TDF+FTC	Ref		Ref	
ABC+3TC	0.41 (0.06-3.03)	0.384	0.20 (0.03-1.55)	0.125
Other*	2.94 (1.15-7.56)	**0.025**	1.72 (0.62-4.78)	0.298
First ART recommended by current guidelines	0.64 (0.31-1.32)	0.227	0.40 (0.18-0.91)	**0.029**
CD4/CD8 (per 1 point increase)	0.24 (0.07-0.85)	**0.027**	0.13 (0.03-0.51)	**0.003**

Taramasso L, et al HIV Medicine 2020

HIV-DNA decrease during treatment in primary HIV-1 infection with 3 different drug regimens: INACTION trial

TABLE 1 Baseline characteristics of enrolled PLWH by treatment arm.

		Randomly assigned treatment arm			
Factors	**Level/unit**	**TAF/FTC + DRV/c *N* = 30**	**TAF/FTC + DTG *N* = 28**	**TAF/FTC + DRV/c + DTG *N* = 20**	***p****
Fiebig (%)	1	1 (3.3)	2 (7.4)	1 (5.6)	0.262
	2	8 (26.7)	4 (14.8)	4 (22.2)	
	3	1 (3.3)	3 (11.1)	0 (0.0)	
	4	6 (20.0)	0 (0.0)	4 (22.2)	
	5	11 (36.7)	13 (48.1)	5 (27.8)	
	6	3 (10.0)	5 (18.5)	4 (22.2)	
Gender (%)	F	3 (10.0)	0 (0.0)	1 (5.0)	0.319
	M	26 (86.7)	28 (100.0)	19 (95.0)	
	Transgender	1 (3.3)	0 (0.0)	0 (0.0)	
Age (median [IQR])		34.99 [29.17, 43.50]	32.76 [28.08, 41.16]	33.16 [26.66, 46.54]	0.832
Days from HIV diagnosis to ART start (median [IQR])		12 [3, 34]	12 [6, 23]	13 [7, 18]	0.990
Risk factor (%)	Bisexual	1 (4.3)	0 (0.0)	0 (0.0)	0.741
	Hetero	1 (4.3)	2 (7.7)	1 (5.6)	
	Homo	5 (21.7)	9 (34.6)	4 (22.2)	
	Transgender	16 (69.6)	15 (57.7)	13 (72.2)	
HCV (%)	No	27 (96.4)	25 (96.2)	19 (100.0)	0.695
	Yes	1 (3.6)	1 (3.8)	0 (0.0)	
CD4 count (median [IQR])	Cells/mm^3	547.00 [397.50, 669.50]	552.00 [394.00, 653.00]	474.00 [430.00, 584.00]	0.875
CD4 percentage (median [IQR])	%	23.10 [18.30, 27.65]	18.00 [11.30, 29.00]	19.00 [15.00, 27.60]	0.477
CD4/CD8 (median [IQR])		0.47 [0.30, 0.59]	0.35 [0.17, 0.58]	0.33 [0.23, 0.50]	0.499
HIV-RNA (median [IQR])	$\log_{10}$(copies/mL)	5.17 [4.40, 6.02]	5.43 [4.27, 6.04]	5.75 [4.83, 6.22]	0.708
HIV-DNA (median [IQR])	$\log_{10}$(copies/10^6 PBMCs)	4.39 [4.08, 4.73]	4.53 [4.22, 4.83]	4.45 [4.11, 4.79]	0.600

Bruzzesi E, et al J Med Virol. 2023

HIV-DNA decrease during treatment in primary HIV-1 infection with 3 different drug regimens: INACTION trial

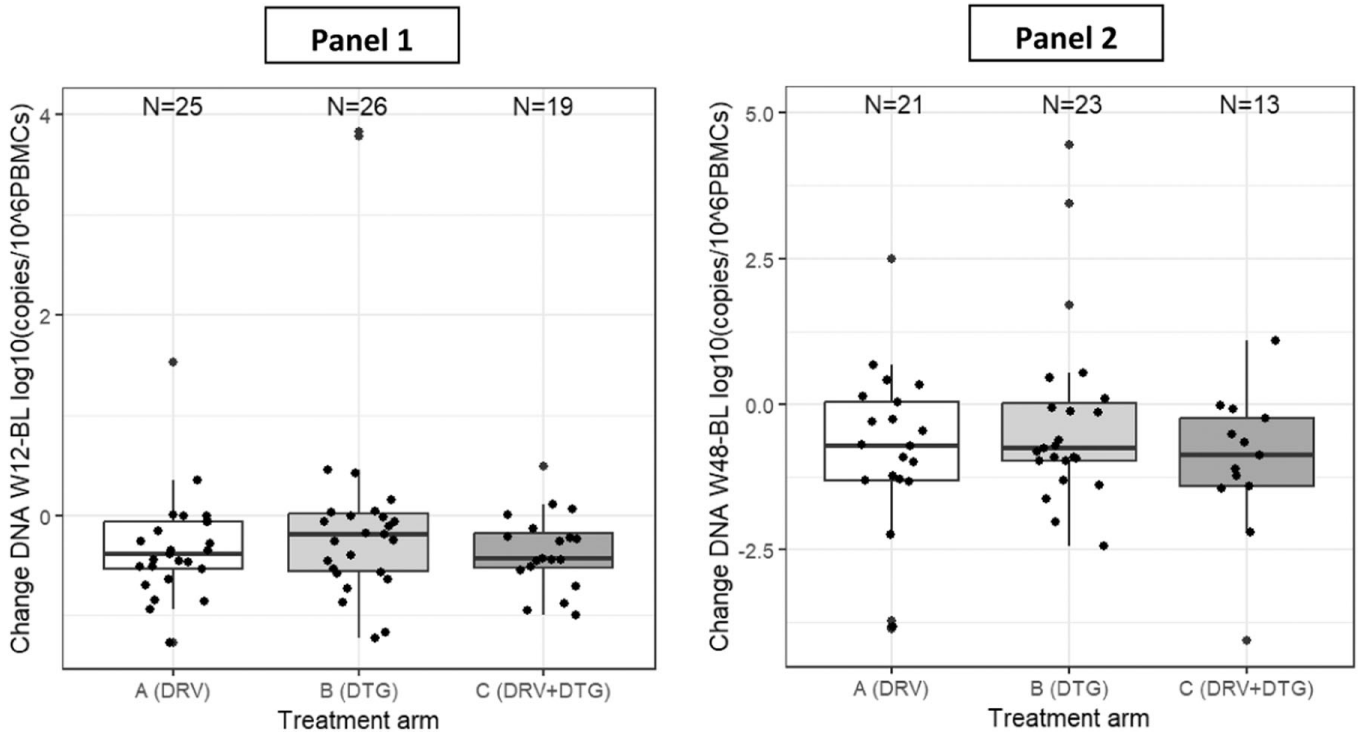
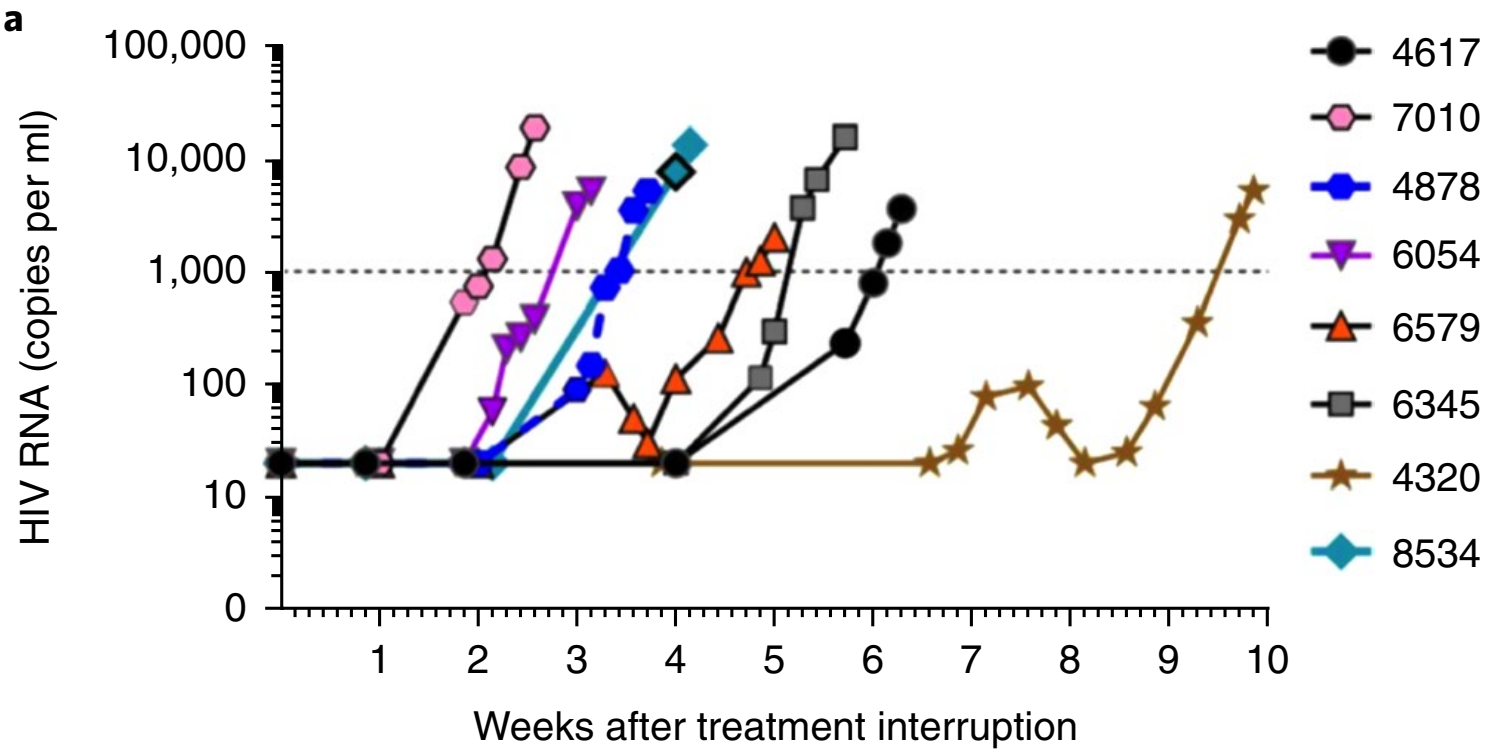


FIGURE 2 Change in HIV-DNA from baseline to W12 (Panel 1) and from baseline to W48 (Panel 2). DRV, darunavir; DTG, dolutegravir; PBMCs, peripheral blood mononuclear cells.

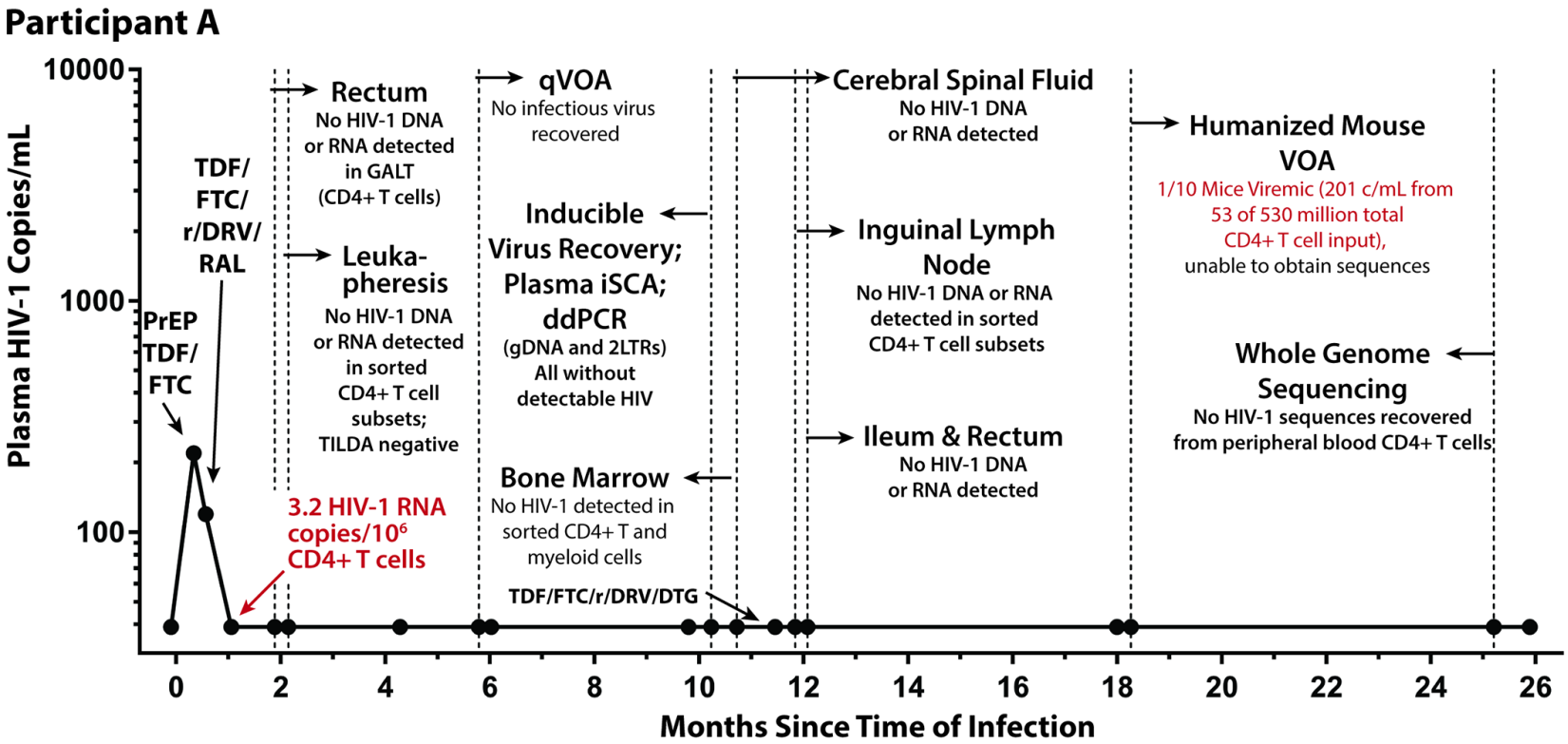
Bruzzesi E, et al J Med Virol. 2023

Rapid HIV RNA rebound after ATI in persons durably suppressed in Fiebig I acute HIV infection



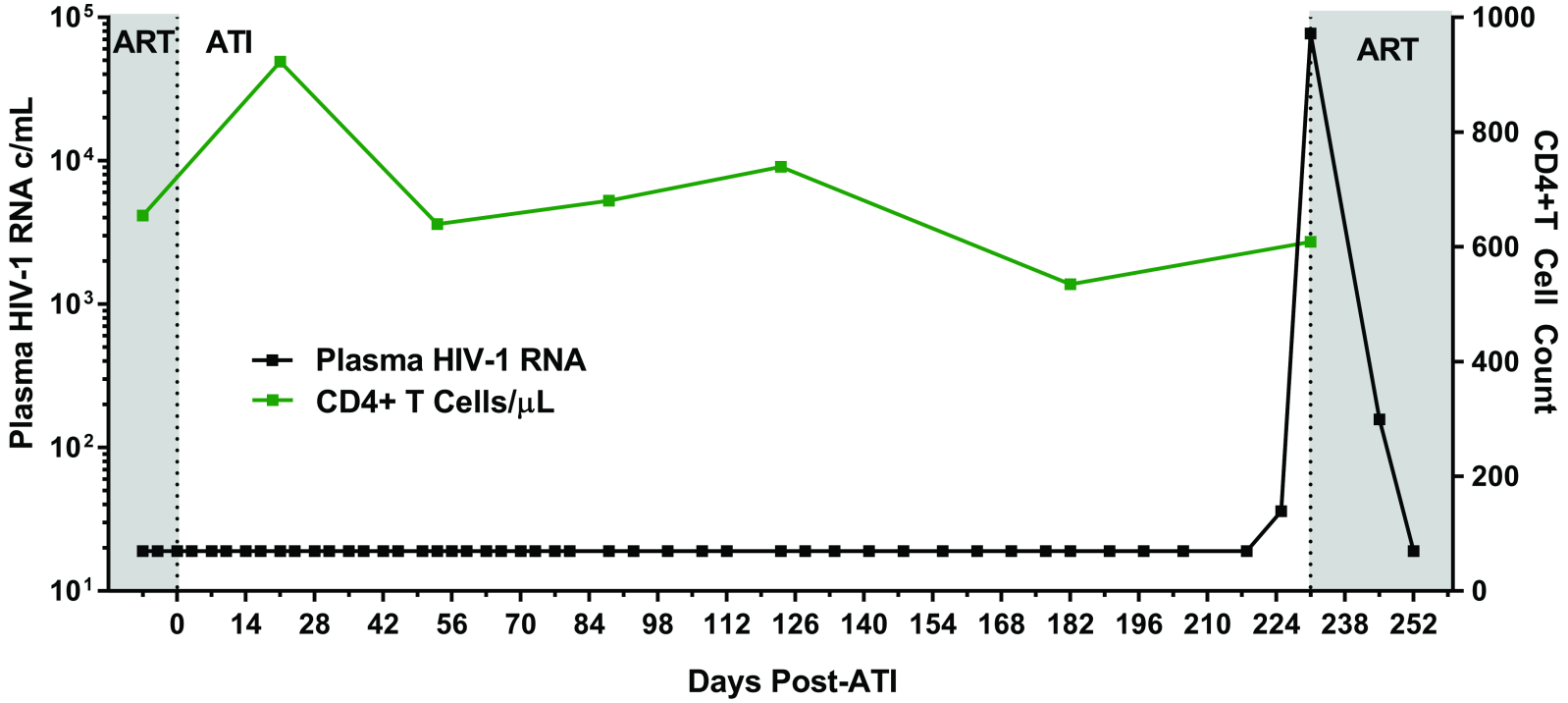
Colby DJ, et al Nat Med 2018

HIV-1 persistence following extremely early initiation of ARTduring acute HIV-1 infection



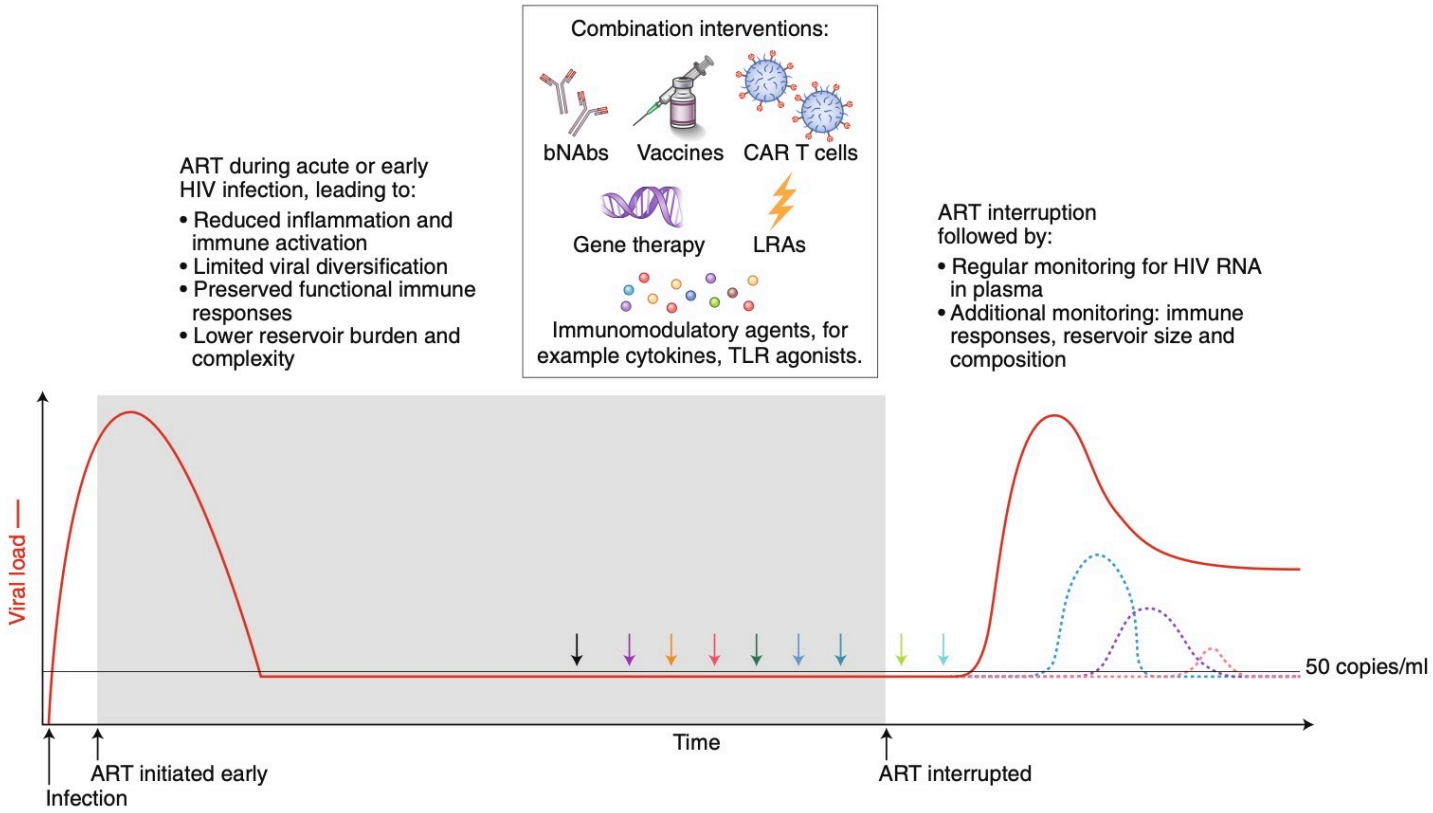
Henrich TJ, et al Plos Med 2018

HIV-1 persistence following extremely early initiation of ARTduring acute HIV-1 infection



Henrich TJ, et al Plos Med 2018

Strategies that will enhance immune-mediated clearance of latently infected cells



Deeks SG, et al. Nat Med 2021

Strategies that will enhance immune-mediated clearance of latently infected cells

Fig 1. Study Schematic

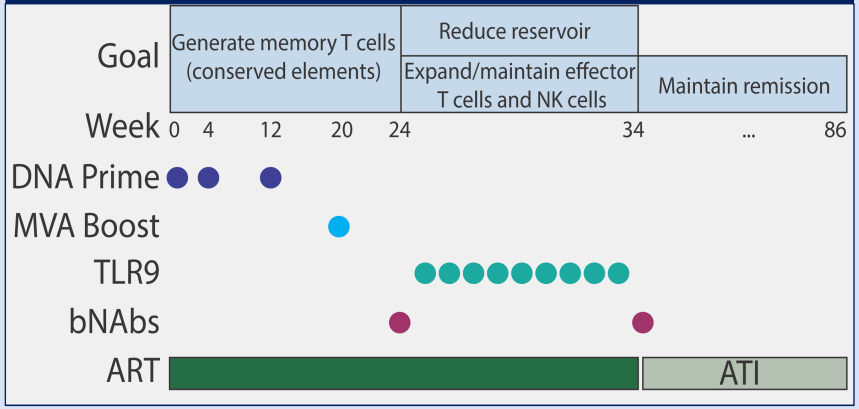


Fig 3. Time to Rebound

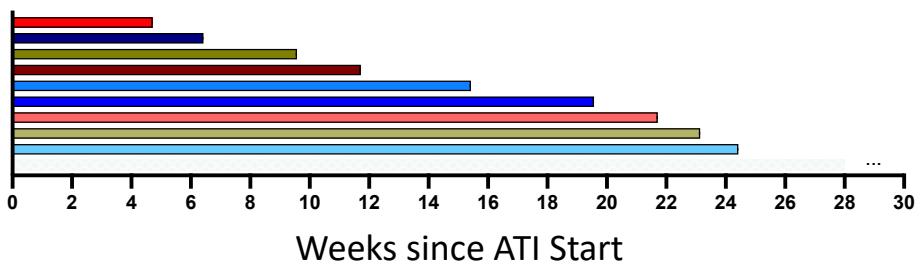


Fig 4. Vaccine-induced T Cell Responses to Conserved Elements

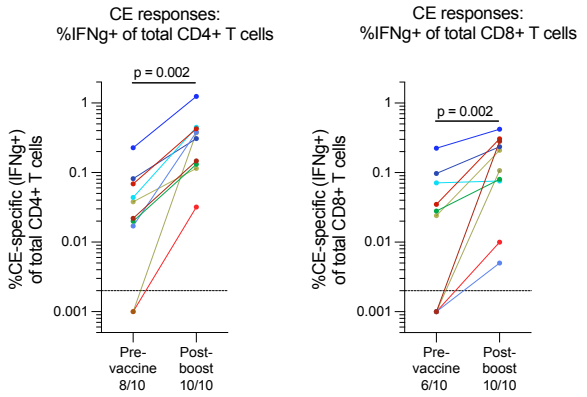
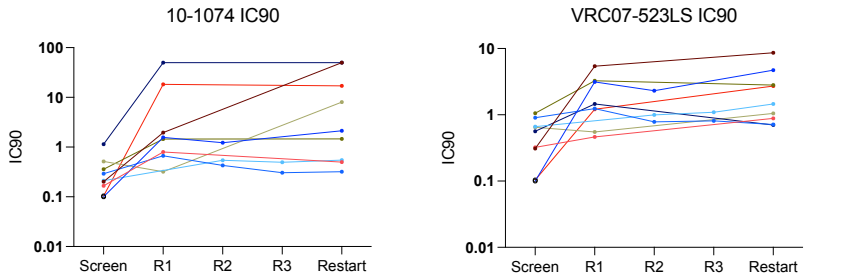


Fig 5. Evolving Phenotypic Susceptibility to bNAbs



Peluso M, et al. CROI 2023

Primary HIV infection during chronic treatment with imatinib: impact on infection dynamics

The participant was put on treatment with imatinib at 100 mg/day in February 2019, for a myeloproliferative neoplasm with eosinophilia.

In January 2022, following unprotected sexual intercourse occurred in December 2021, he experienced acute retroviral syndrome.
He tested positive for HIV (Fiebig stage 5),
HIV-RNA at diagnosis >10^7 copies/ml). CD4+ T-cell count at diagnosis was 427/mcL (28%, CD4/CD8 0.46).

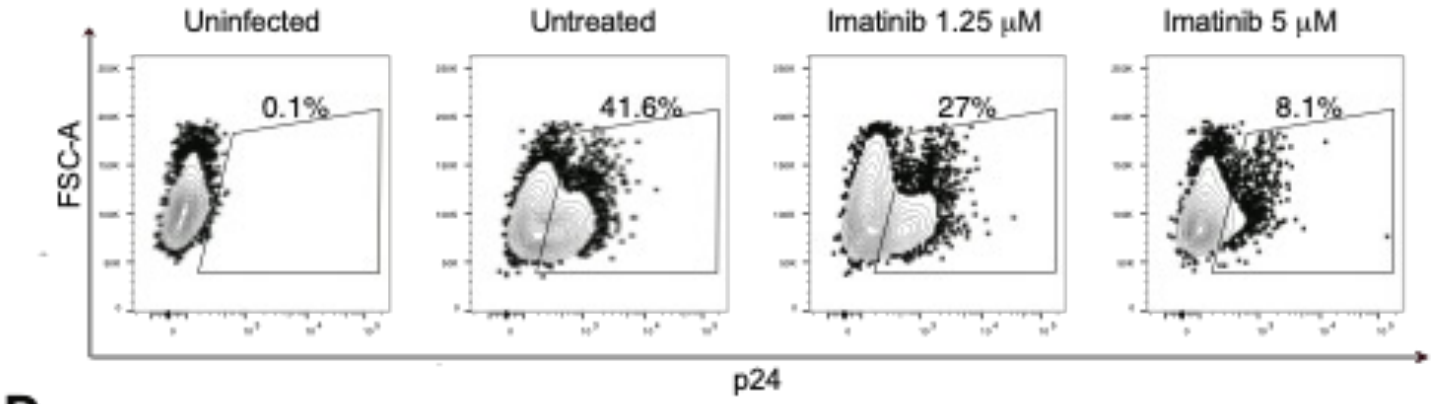
cART was started 7 days after diagnosis.

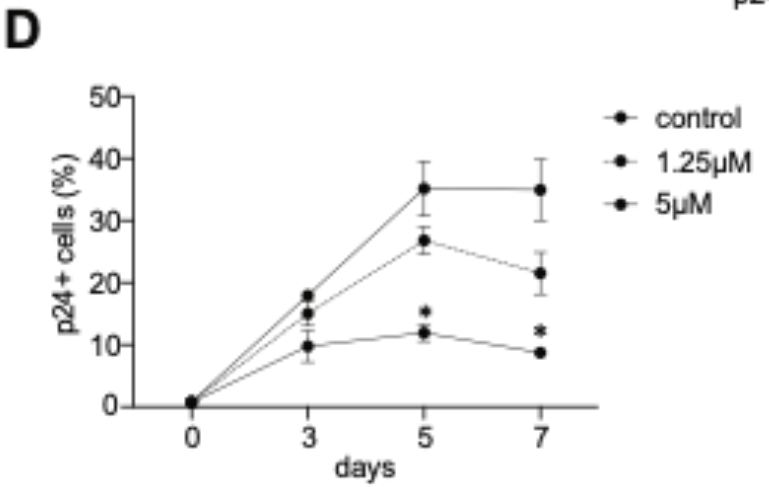
Viral load was 10^2 at 1 month from cART start and reached undetectable levels by six months,
CD4 count at six months was 1172/mcL (56%, CD4/CD8 2).

Quantification of HIV DNA in isolated CD4+ T cells was performed via digital droplet PCR: 3.7x10^4 HIV-1 DNA copies/10^6 CD4+ T cells before ART initiation and 6.6x10^2 copies/10^6 cells after one year of ART

Bozzi G, et al. submitted

Primary HIV infection during chronic treatment with imatinib: impact on infection dynamics





Bozzi G, et al. submitted

Conclusions

Events during acute HIV-1 infection may modulate the long-term course of HIV-1 disease.

Acute and early HIV-1 infection is a major contributor to the epidemic spread of HIV-1 and limiting this spread through “test and treat” strategies may require treatment of persons during the acute phase of infection.

The HIV-1 reservoir, which confounds efforts to cure infection, may be more responsive to antiviral therapy during acute HIV-1 infection than during chronic infection.

Intervention during AHI could dramatically reduce epidemic spread, reduce the size of the HIV-1 reservoir, and potentially achieve long-term control of plasma viremia without the use of long- term antiviral treatment

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