Potential post-treatment controllers: the time is now

Francesca Bai

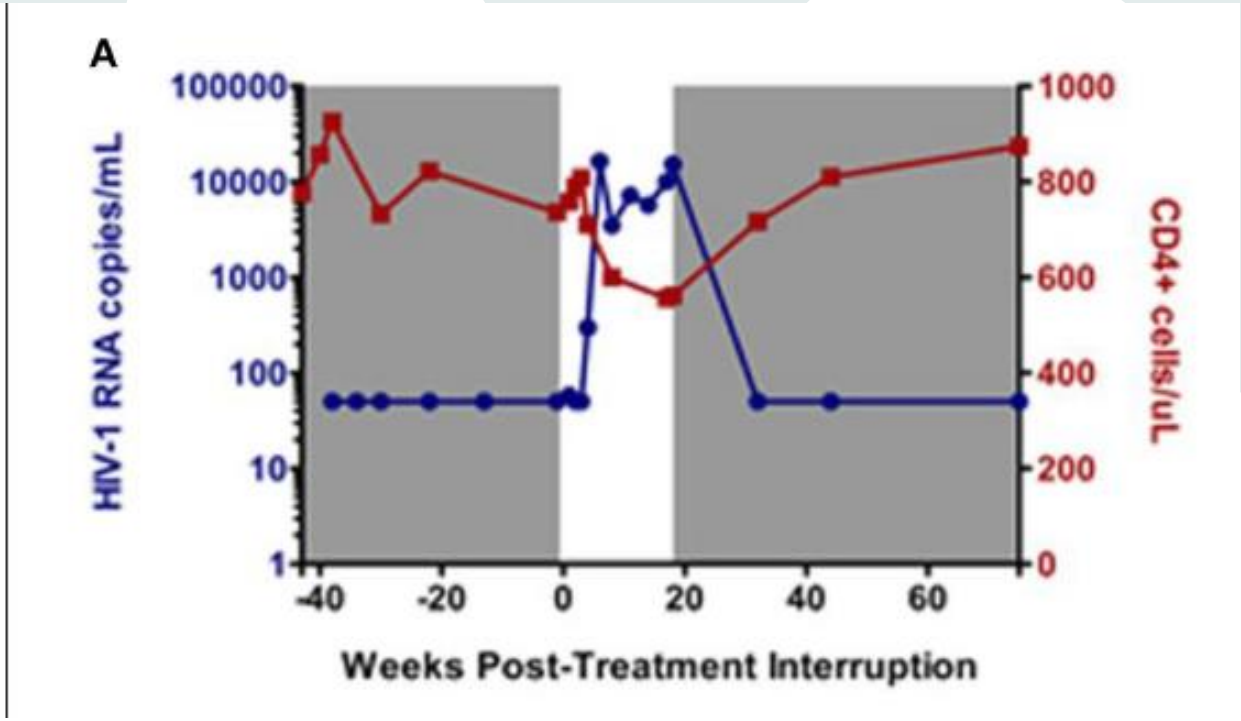
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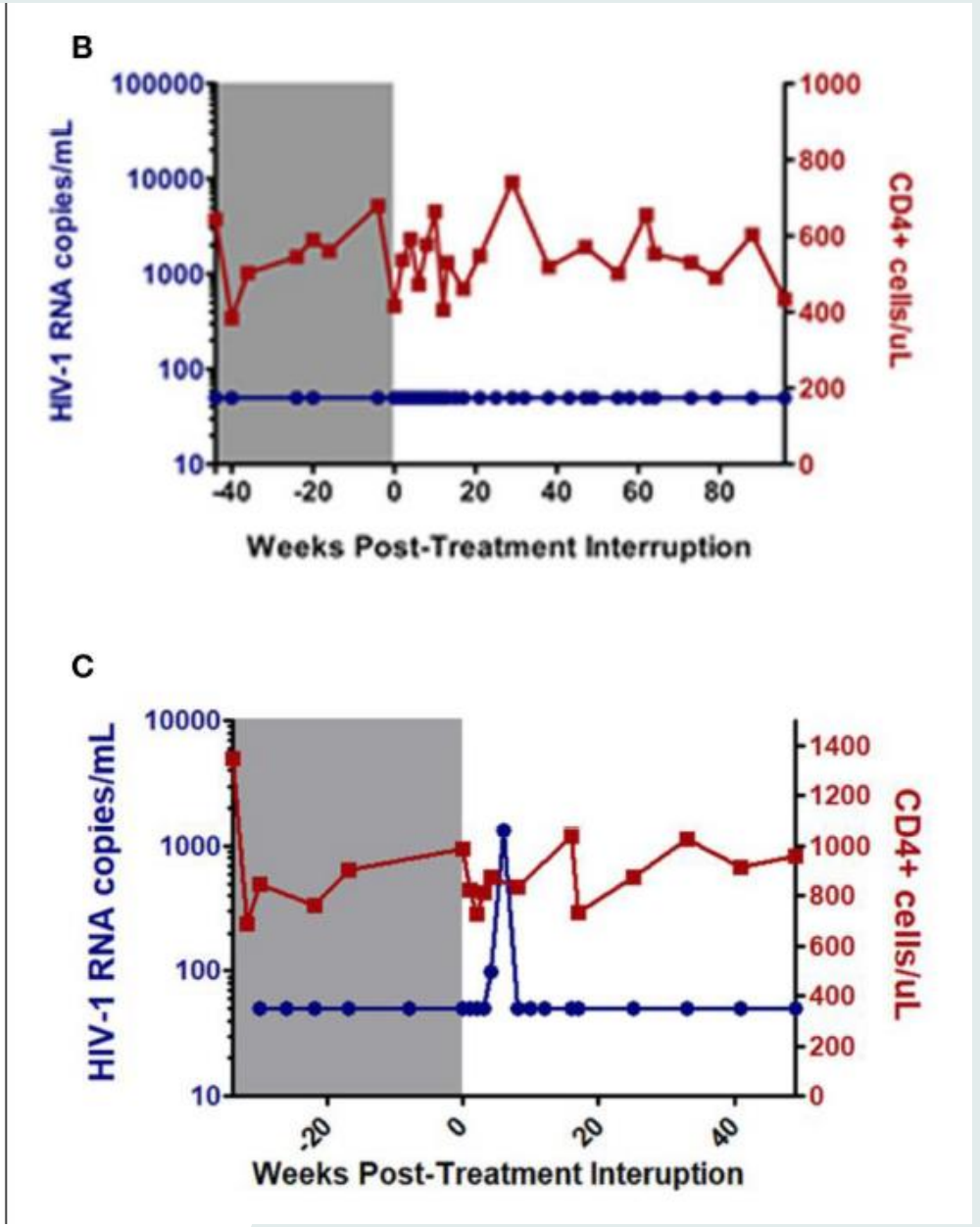
Outline

- Phenotypical characteristics of PTCs: lessons from the cohorts of PTCs
- Potential post treatment controllers (PPTCs): which clinical and viro-immunological characteristics really matter? Lessons from Analytical treatment interruptions (ATI) studies
- Potential biomarkers of viral rebound after ATI and of PTCs phenotype

Non controllers



Post-treatment controllers



Etemad B et al, Frontiers in Immunology 2019; 10; 1749

VISCONTI cohort

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1]*, Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5]*, the ANRS VISCONTI Study Group[¶]

- The VISCONTI study was one of the earliest and most comprehensive of the PTC studies

- The inclusion criteria for the **14 VISCONTI participants** were individuals who were treated during early HIV infection and maintained viral suppression <400 HIV-1 RNA copies/mL for at least 2 years after ART interruption.

Control of HIV after Antiretroviral Medication Pause (CHAMP) cohort

- **67 PTCs** (pooled analysis of 14 ACTG studies and other North American cohorts)
- Individuals who maintained viral loads ≤400 copies/mL at **≥2/3** or more of time points for **≥24 weeks** post interruption
- 45% had early viral load peaks 1,000 HIV-1 RNA copies/mL and 33% had early viral load peaks 10,000 HIV-1 RNA copies/mL
- Proportion of PTCs who remained virologically suppressed in years 1–5 were **75, 55, 41, 30, and 22%**, respectively

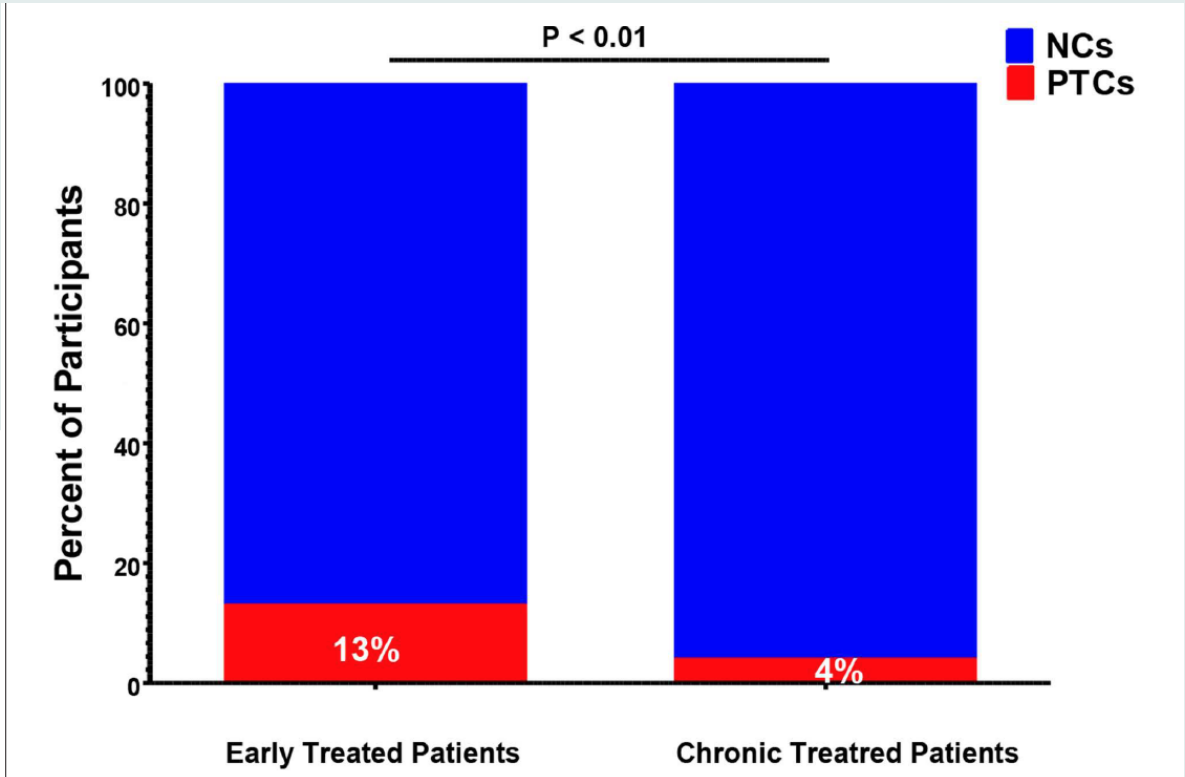


FIGURE 2 | Frequency of post-treatment controllers (PTCs) identified in early- vs. chronic-treated participants of the CHAMP study (6). NCs, post-treatment non-controllers.

PCT: demographic data

- The median age of PTCs ranged from **27 to 46 years old**.
- The majority of PTCs identified were males, likely reflecting the sex distribution of the clinical trial participants; there have been reports that **female gender** may be associated with a higher chance of post-treatment HIV control and spontaneous control
- Majority of PTCs have been reported by studies from North America and Europe
- African participants tended to have lower pre-ART viral load and integrated HIV-DNA levels, and after treatment interruption, **Africans** appeared to experience a longer duration of viral remission than non-Africans in the SPARTAC study

Etemad B et al, Frontiers in Immunology 2019; 10; 1749

PCT: immuno-virological data

- **CD4+** cell counts for the PTCs were generally **quite high** with a median of 720 to 1,429 cells/mm3

- The median time of **HIV rebound after ART interruption** for ***post-treatment non-controllers*** (NCs) is **3–4 weeks** and only a small proportion of non-controllers are able to maintain viral suppression to 12 weeks or beyond

- The duration of viral control after treatment interruption has also differed dramatically between studies and ranged from a median of **6 months to more than 2-10 years**

Spontaneous and post-treatment controllers

- SCs generally harbor **replication competent virus** and have evidence of ongoing viral replication and evolution;
- The ongoing viral replication in SCs may be associated with progressive loss of CD4+ T cells, **increased T cell activation and inflammation**
- Protective effects of **HLA B∗27** and **B∗57**
- Low Gag-specific CD8+ T cell response, high levels of inflammatory cytokines and high viral diversity have been reported as factors that predict loss of viral control in ECs

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Differences PTCs and SCs/ECs

(1) CD8+ CTL and HIV-specific CD8+ T cell responses responses have been found to be far weaker in PTCs;

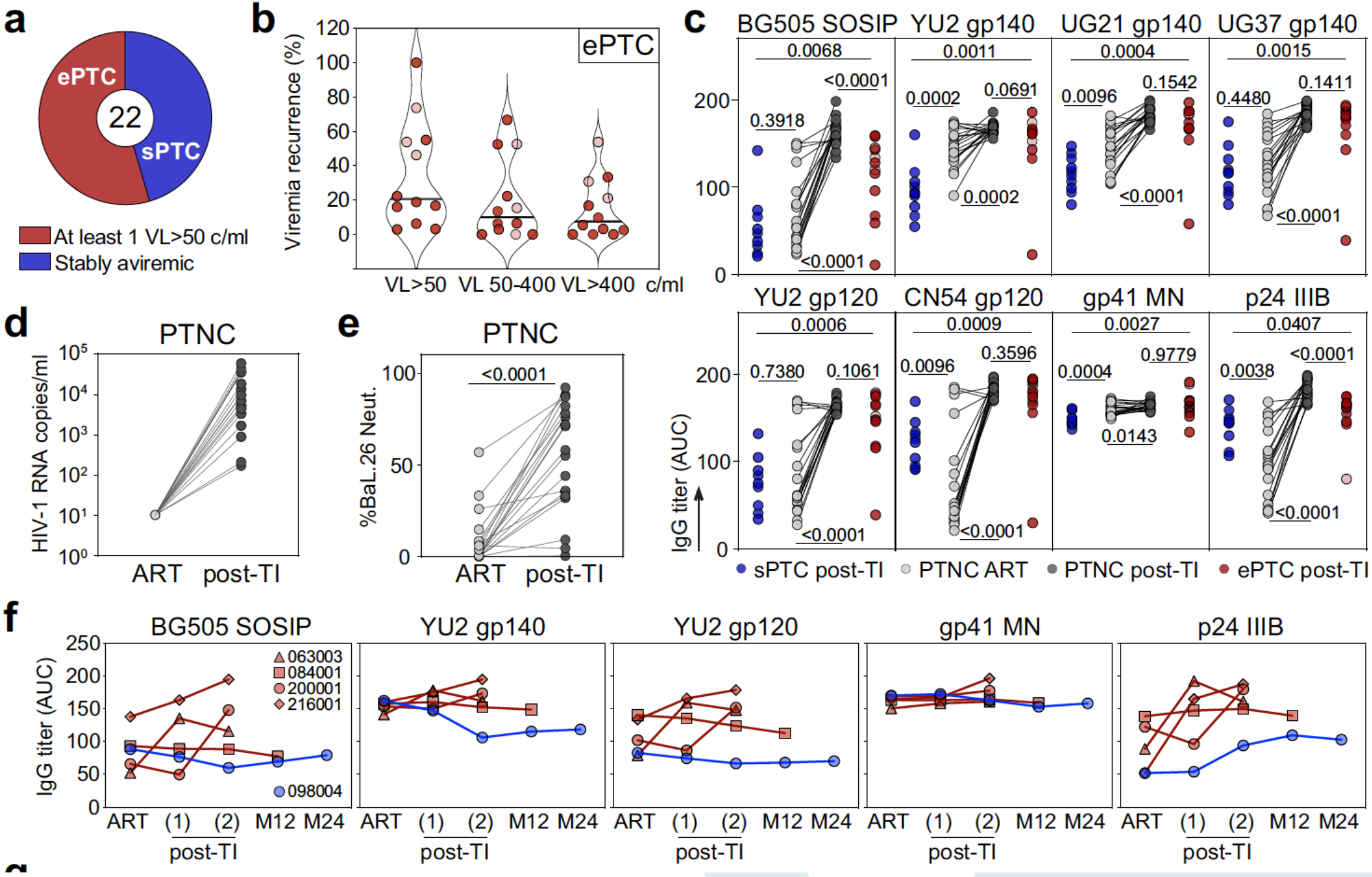
(2) PTCs do not tend to harbor protective HLA alleles;

(3) PCT not exhibit the same heightened levels of immune activation as SCs

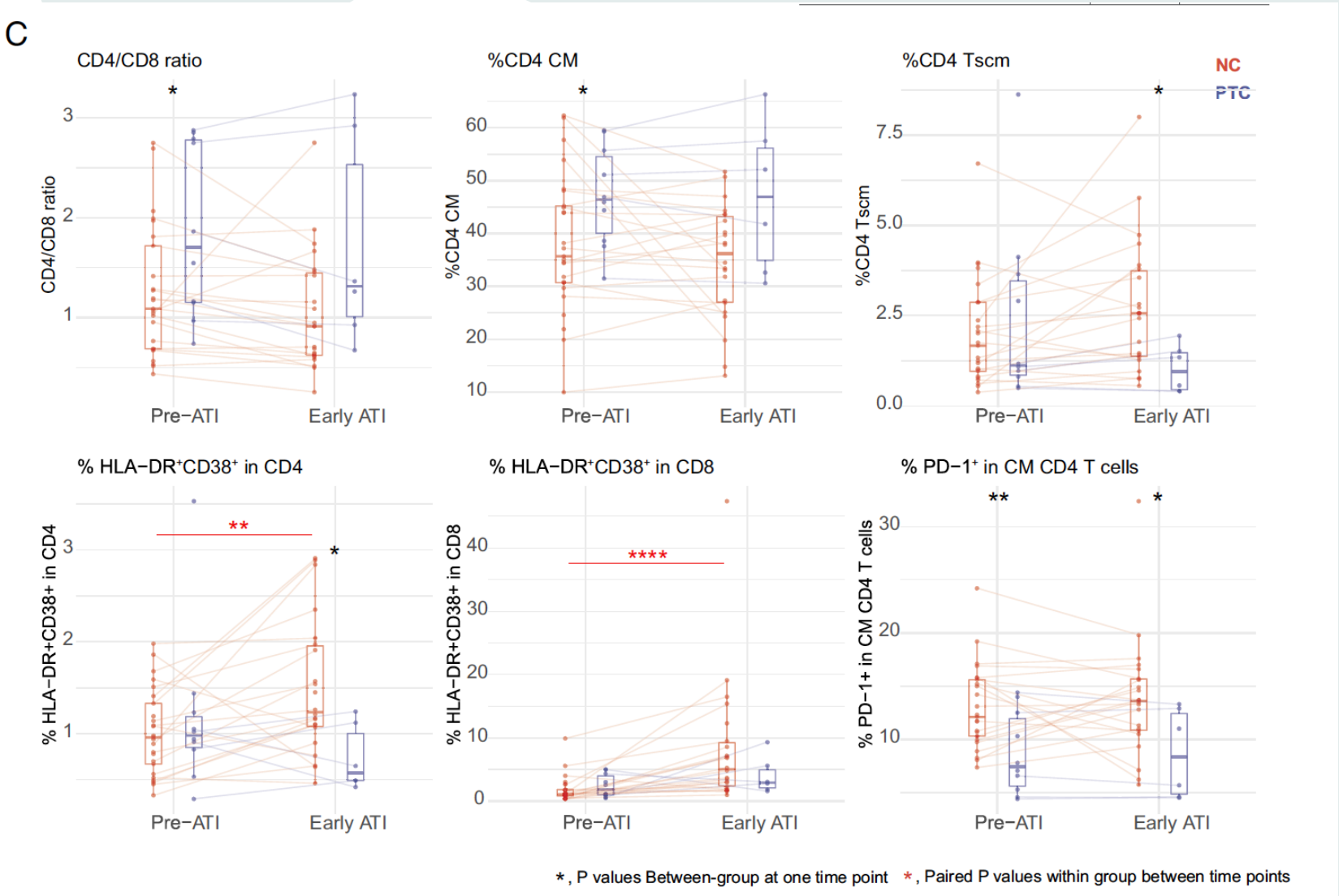
(4) Pre-ART viral loads are generally significantly higher in PTCs;

(5) PTCs frequently present with symptomatic acute retroviral syndrome;

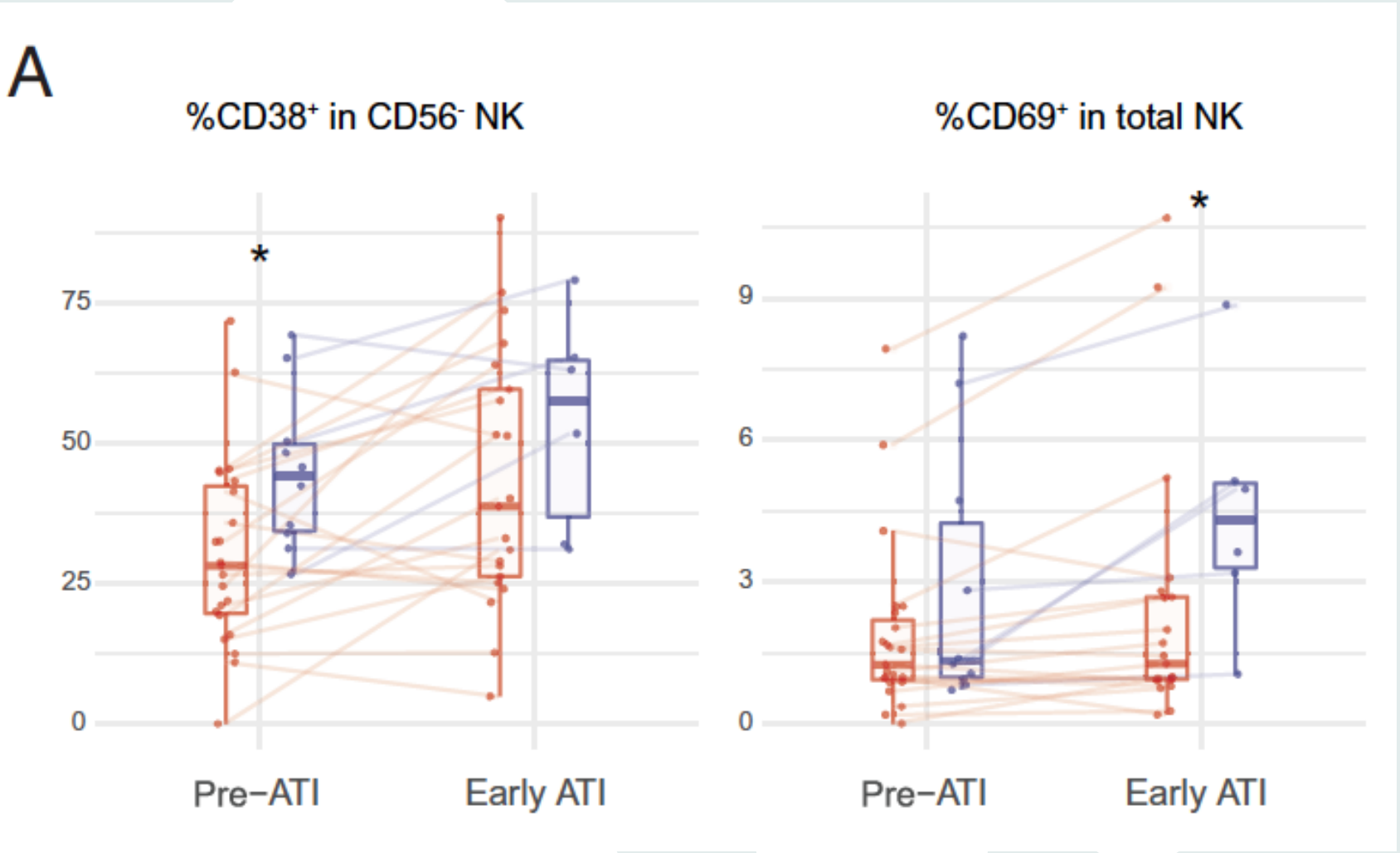
Etemad B et al, Frontiers in Immunology 2019; 10; 1749


a
ePTC
22
sPTC
At least 1 VL>50 c/ml
Stably aviremic
b
ePTC
Viremia recurrence (%)
VL>50
VL 50-400
VL>400
c/ml
c
BG505 SOSIP
YU2 gp140
UG21 gp140
UG37 gp140
YU2 gp120
CN54 gp120
gp41 MN
p24 IIIB
IgG titer (AUC)
sPTC post-TI
PTNC ART
PTNC post-TI
ePTC post-TI
d
PTNC
HIV-1 RNA copies/ml
ART
post-TI
e
PTNC
%BaL.26 Neut.
ART
post-TI
f
BG505 SOSIP
YU2 gp140
YU2 gp120
gp41 MN
p24 IIIB
IgG titer (AUC)
063003
084001
200001
216001
098004
ART
(1)
(2)
M12
M24
post-TI

Immunologically, PTCs demonstrated significantly higher CD4+ T cell% and CD4+/CD8+ ratio, lower CD4+ and CD8+ T cell activation, lower CD4+ T cell exhaustion



Sparse partial least squares discriminant analysis identified a set of features enriched in PTCs, including a more functional NK cells.

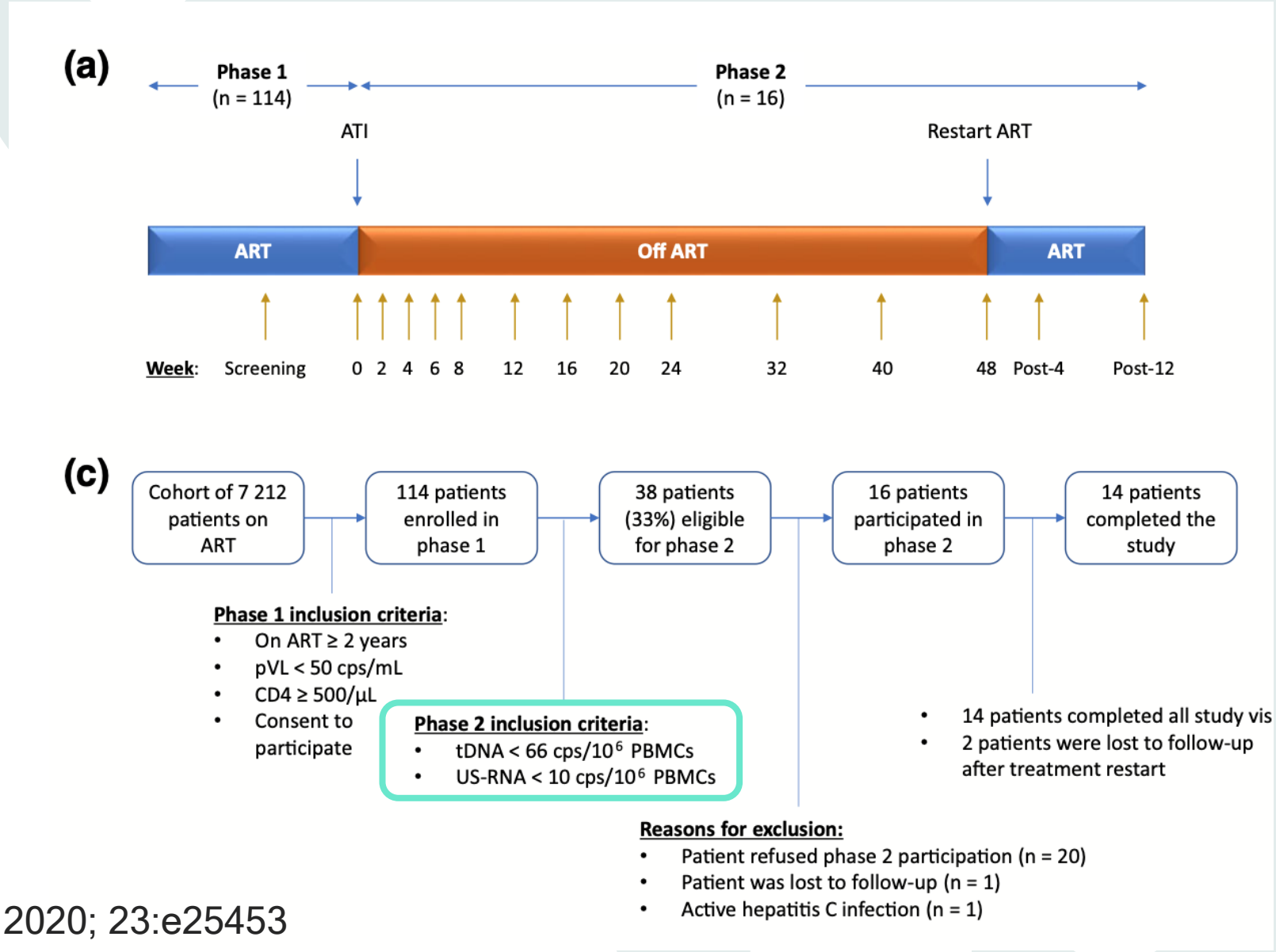


Smaller HIV reservoir in PCT

- Levels of pre-treatment interruption HIV proviral DNA / lower levels of cell-associated HIV-RNA predicted viral rebound
- PTCs had an **~7-fold smaller HIV reservoir** compared to NCs prior to the ATI, but that some PTCs had relatively large fractions of intact proviruses
- The restricted size of the reservoir, including the intact proviral genomes, however, **does not fully explain post-treatment control**
- Additional studies are needed to assess potential differences in the distribution of infected cell types, cellular transcription environment, integration sites, and other factors that could contribute to the maintenance of a “deeper” state of viral latency

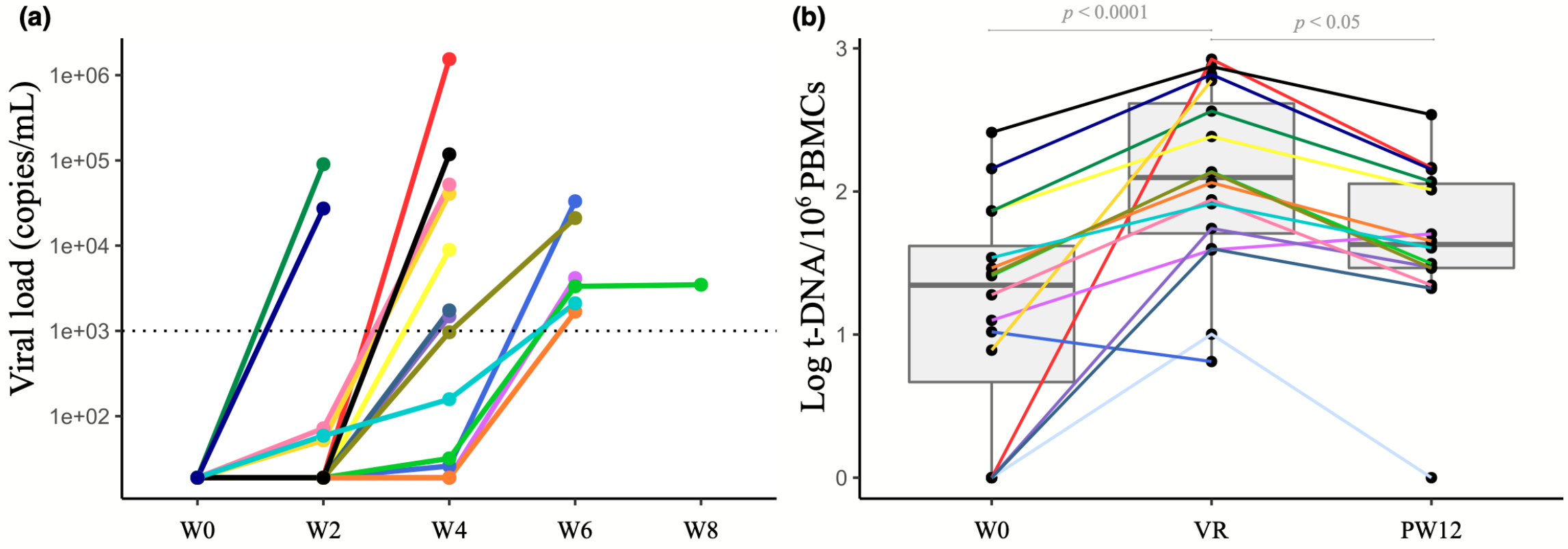
Etemad B et al, Frontiers in Immunology 2019; 10; 1749

Rapid viral rebound after ATI in patients with very small HIV reservoir



Pannus P et al, JIAS 2020; 23:e25453

Rapid viral rebound after ATI in patients with very small HIV reservoir



PW12: 12 weeks after restart ART; VR, timepoint at viral rebound just before restart ART, W, weeks; W0, timepoint at stop ART

Pannus P et al, JIAS 2020; 23:e25453

Castagna A et al, JAC 2019; 74:2039-2046

APACHE study

The study included adults with HIV-1 chronic infection, followed up at San Raffaele Hospital, with HIV-1 RNA <50 copies/mL for ≥10 years, without single viral blips (HIV-1 RNA >50 copies/mL) during the 10 years before the screening, absence of plasma residual viraemia (RV) for ≥5 years before the screening, current CD4+ >500 cells/mm^3 and HIV-DNA <100 copies/10^6 PBMCs.

We excluded patients based on the following criteria: not adopting effective prophylactic measures (i.e. sexual intercourse without use of condoms); pregnant, wishing to be pregnant and breastfeeding women; HCV or HBV co-infected; with a current AIDS-defining event; with a previous diagnosis of diabetes or cancer or major adverse cardiac events (MACE); currently receiving chemotherapy or immuno-modulating agents; with a history of or current psychiatric disorders; and active illicit drug use or alcohol dependence.[16,17] Patients with a history of HIV-related thrombocytopenia or HIV-associated nephropathy or with a current glomerular filtration rate (e-GFR) <50 mL/min/1.73 m^2 were also excluded.

Castagna A et al, JAC 2019; 74:2039-2046

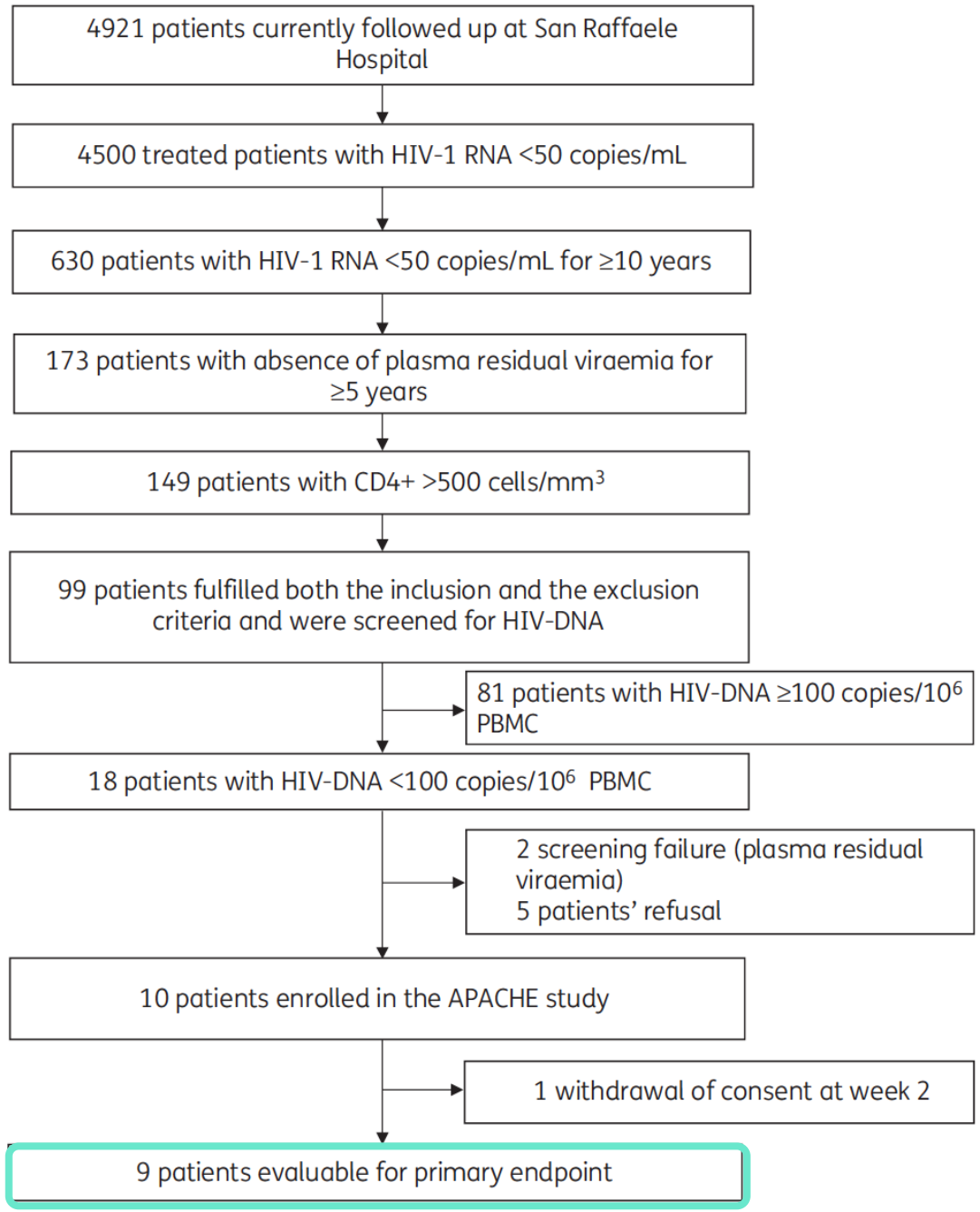
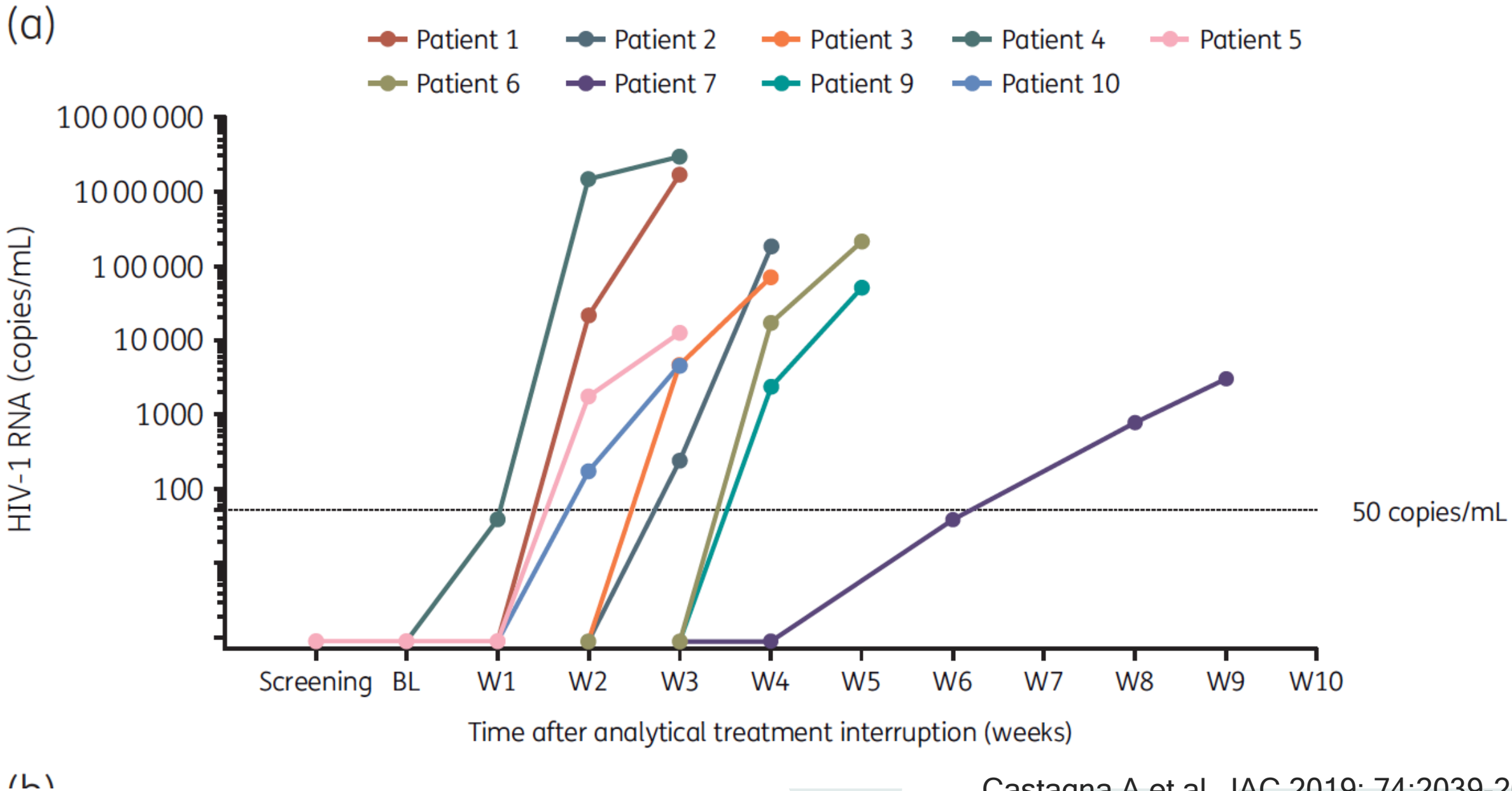


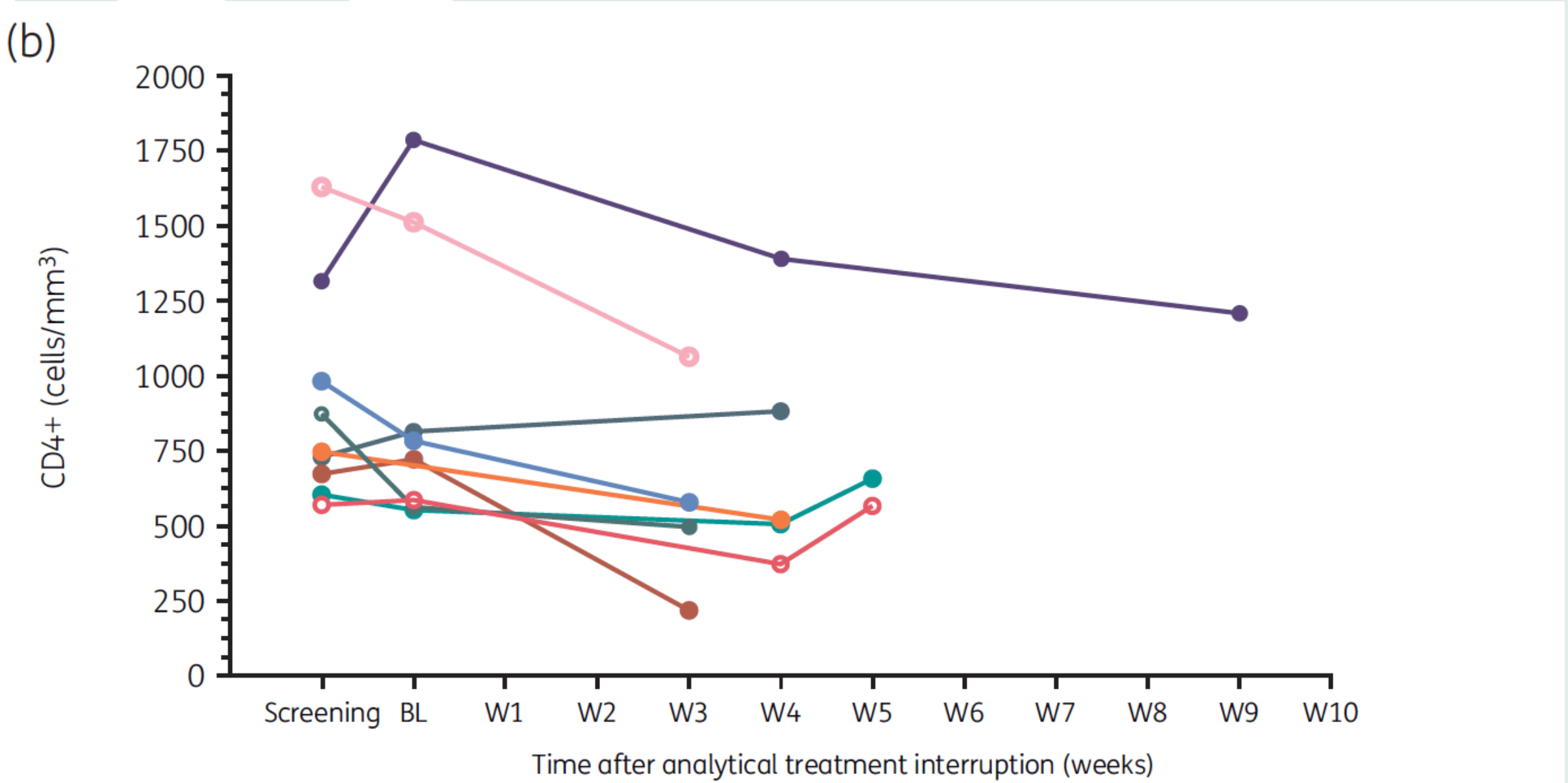
Figure 1. Flowchart of patient selection (data freezing 1 June 2016).

Table 1. Characteristics of the patients who underwent ATI

Characteristic	Median (IQR) or *n* (%)
Age (years)	50.7 (48.1–62.5)
Male sex	9 (90)
HCV co-infection	0 (0)
Previous AIDS diagnosis	1 (10)
Years since HIV diagnosis	17.0 (15.2–21.0)
Time between HIV diagnosis and ART start (months)	7.1 (1.0–51.5)
Time since ART start (years)	16.9 (13.2–18.2)
Pre-ART HIV-1 RNA (copies/mL)	61 000 (13 378–423 501)
$\log_{10}$ copies/mL	4.79 (4.13–5.63)
Time with HIV-1 RNA <50 copies/mL (years)	11.8 (10.9–12.3)
Absence of plasma RV (years)	7.1 (6.4–7.5)
Nadir CD4+ (cells/μL)	353 (212–402)
CD4+ (cells/mm^3)	737 (586–814)
CD4%	38.1 (26.7–48.8)
CD8+ (cells/mm^3)	743 (284–1235)
CD8%	25.5 (21.6–43.3)
CD4+/CD8+ ratio	1.62 (0.63–2.15)
Co-receptor tropism (false-positive rate) by the G2P algorithm (%)	11.4 (1.7–31.1)



Castagna A et al, JAC 2019; 74:2039-2046



Castagna A et al, JAC 2019; 74:2039-2046

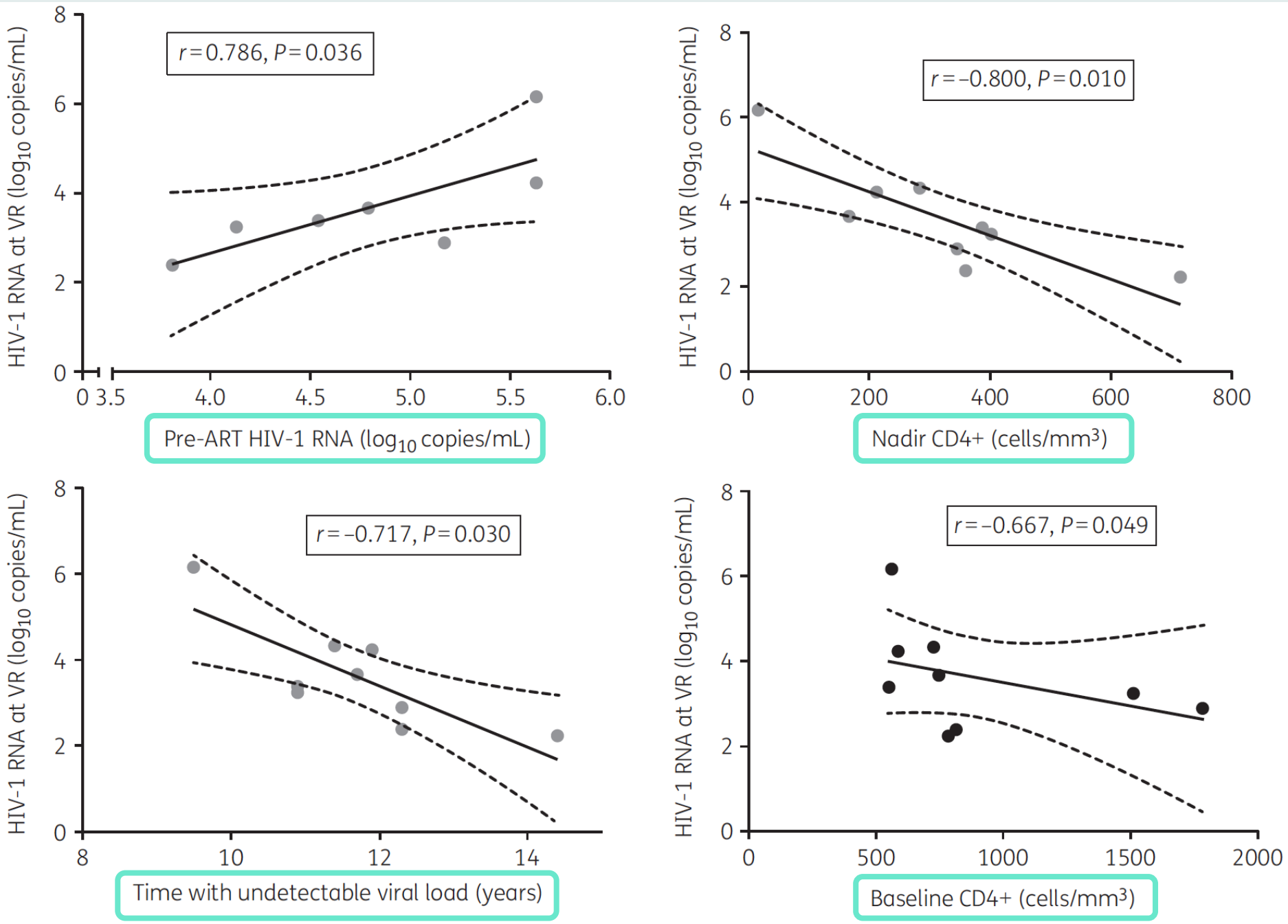
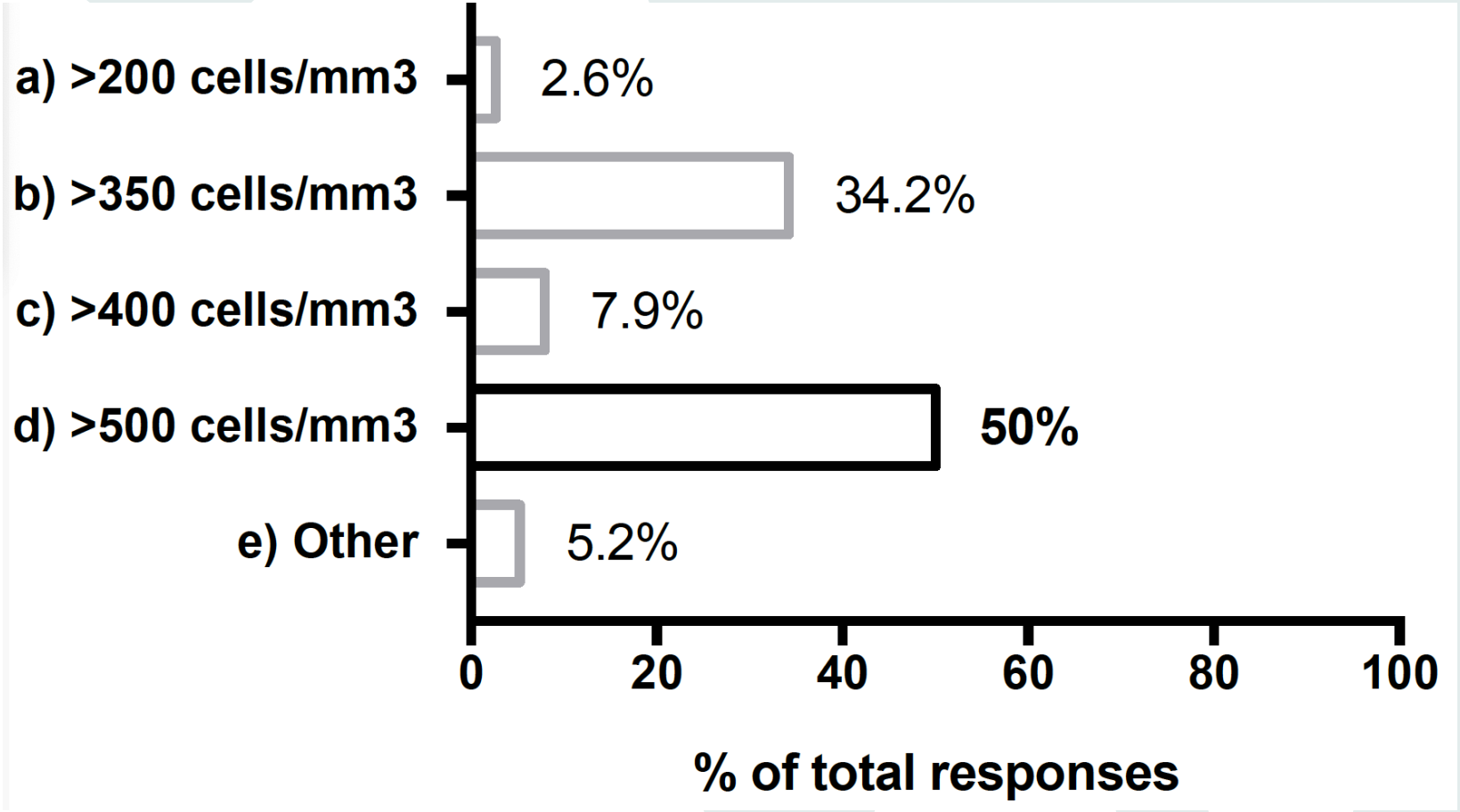


Figure 4. Associations between baseline characteristics and magnitude of viral rebound during ATI. VR, viral rebound.

In summary, we observed that in chronically HIV-1-infected subjects, factors such as long-term suppression of HIV-1 RNA by ART, absence of plasma RV and low HIV-DNA do not confer on the host the ability for spontaneous control of viral replication once antiretroviral drug therapy is withdrawn. On the contrary, the positive impact of both the pre-ART individual profile and the prolonged suppressive ART, in limiting the magnitude of viral recrudescence, may inform future HIV remission studies in chronically infected people living with HIV-1 infection.

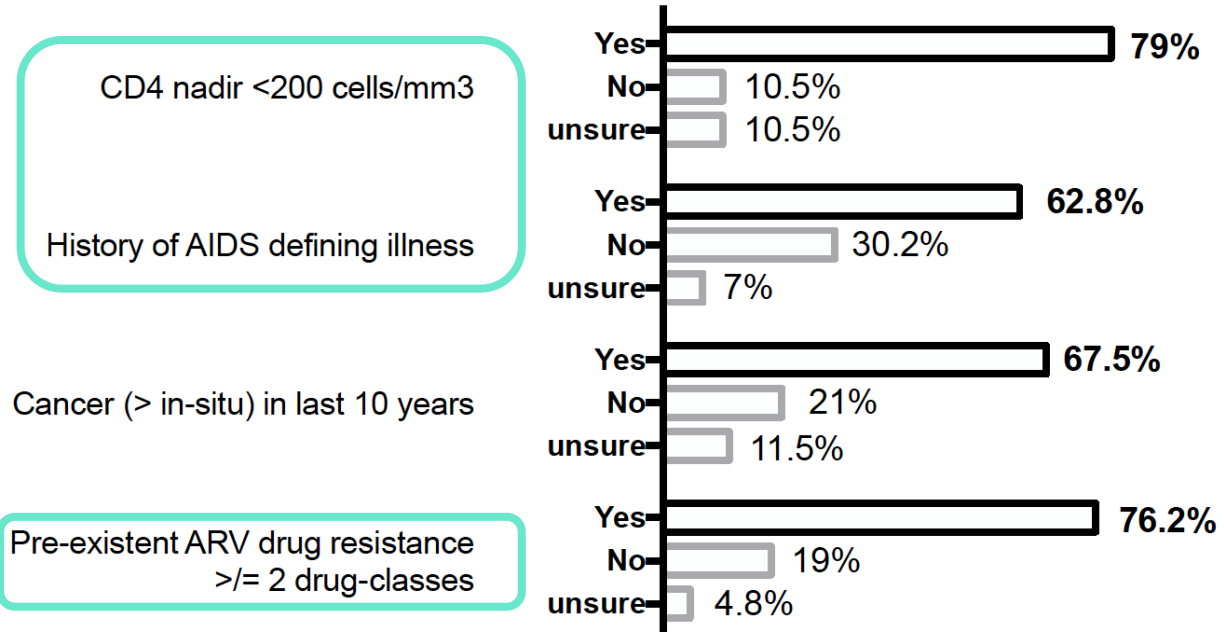
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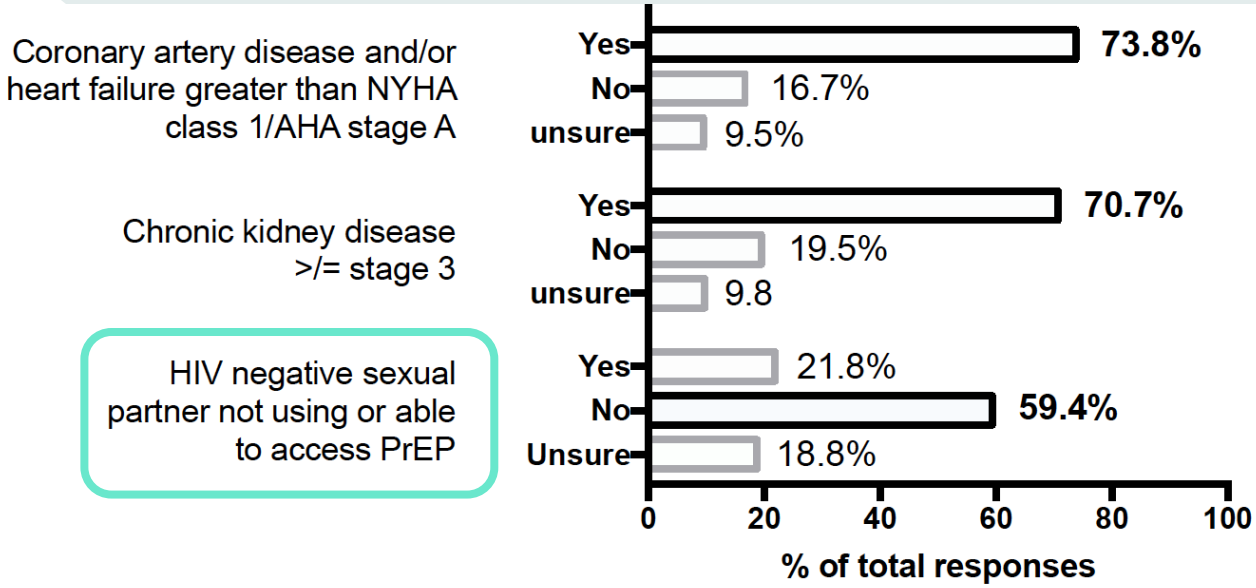
What current CD4+ T-cell count threshold should be used as an inclusion criterion for ATI studies?



Julg B et al, Lancet HIV 2019; 6(4): e259-e268

What should be exclusion criteria for ATI studies?





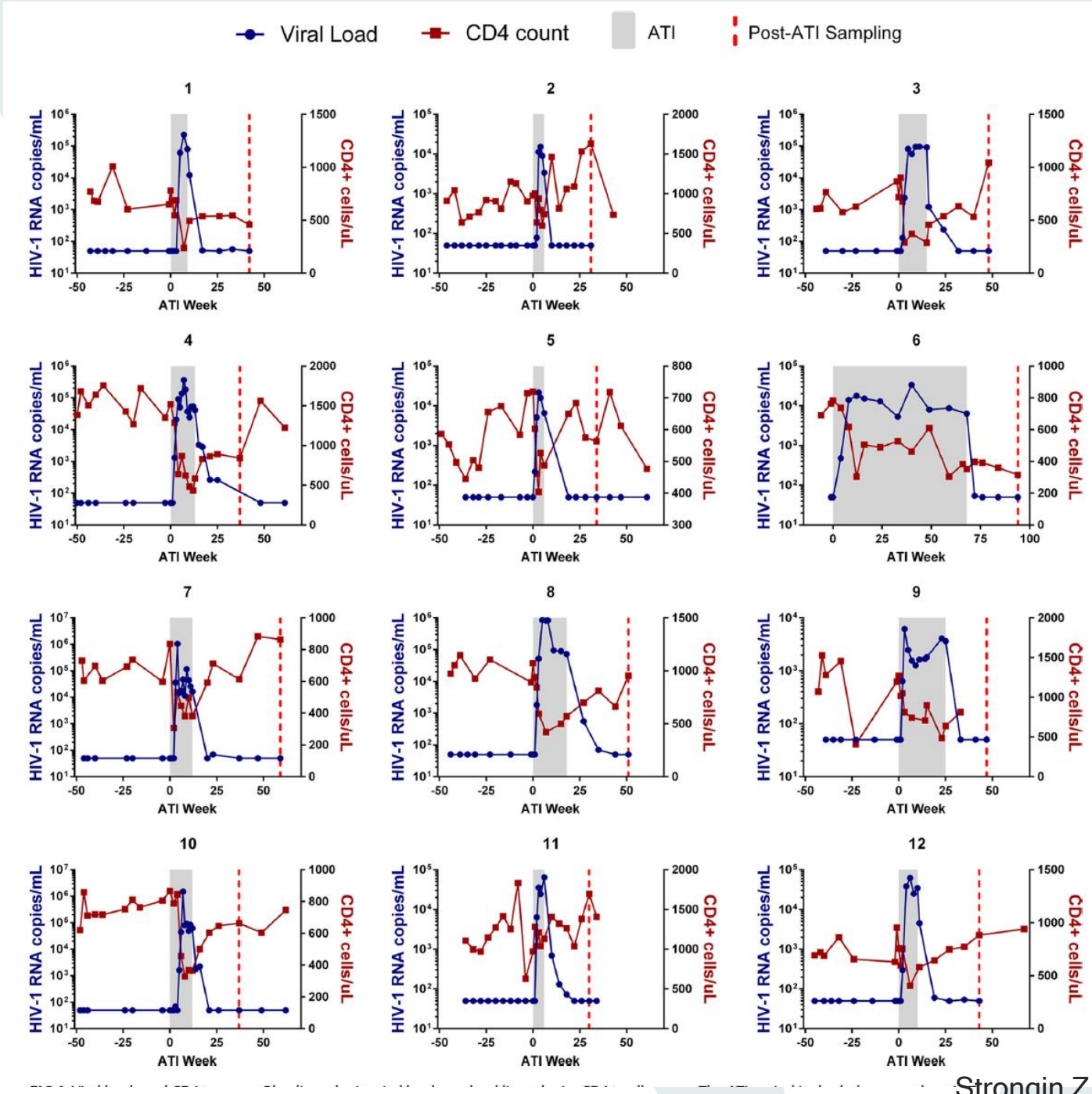
Julg B et al, Lancet HIV 2019; 6(4): e259-e268

Potential impact of an ATI on the size of the reservoir?

Participant	ART duration prior to ATI (yrs)	ATI duration (wks)	ART duration post-ATI (wks)	Infection phase upon ART start	Plasma viral load prior to ATI (copies/ml)	CD4$^+$ count prior to ATI (per mm^3)
1	8.7	9	33	Chronic-treated	<50	780
2	1.1	6	25	Early-treated	<50	979
3	3.7	16	33	Chronic-treated	<50	718
4	7.2	13	24	Chronic-treated	<50	1,520
5	1.1	6	28	Early-treated	<50	719
6	3.2	68	26	Chronic-treated	<50	783
7	12.1	12	47	Chronic-treated	<50	836
8	6.4	18	33	Chronic-treated	<50	1,073
9	6.2	25	22	Chronic-treated	<50	1,270
10	3.3	12	25	Chronic-treated	<50	867
11	1.0	6	24	Early-treated	<50	972
12	4.1	10	33	Chronic-treated	<50	758
Median	3.9	12.0	27.0			851.5

- ACTG studies; assay that uses an automated DNA size-selection platform for quantifying levels of integrated HIV DNA and is less sample- and labor-intensive than current assays.

Strongin Z et al, J Virology 2018; 92(12): e000285



Strongin Z et al, J Virology 2018; 92(12): e000285

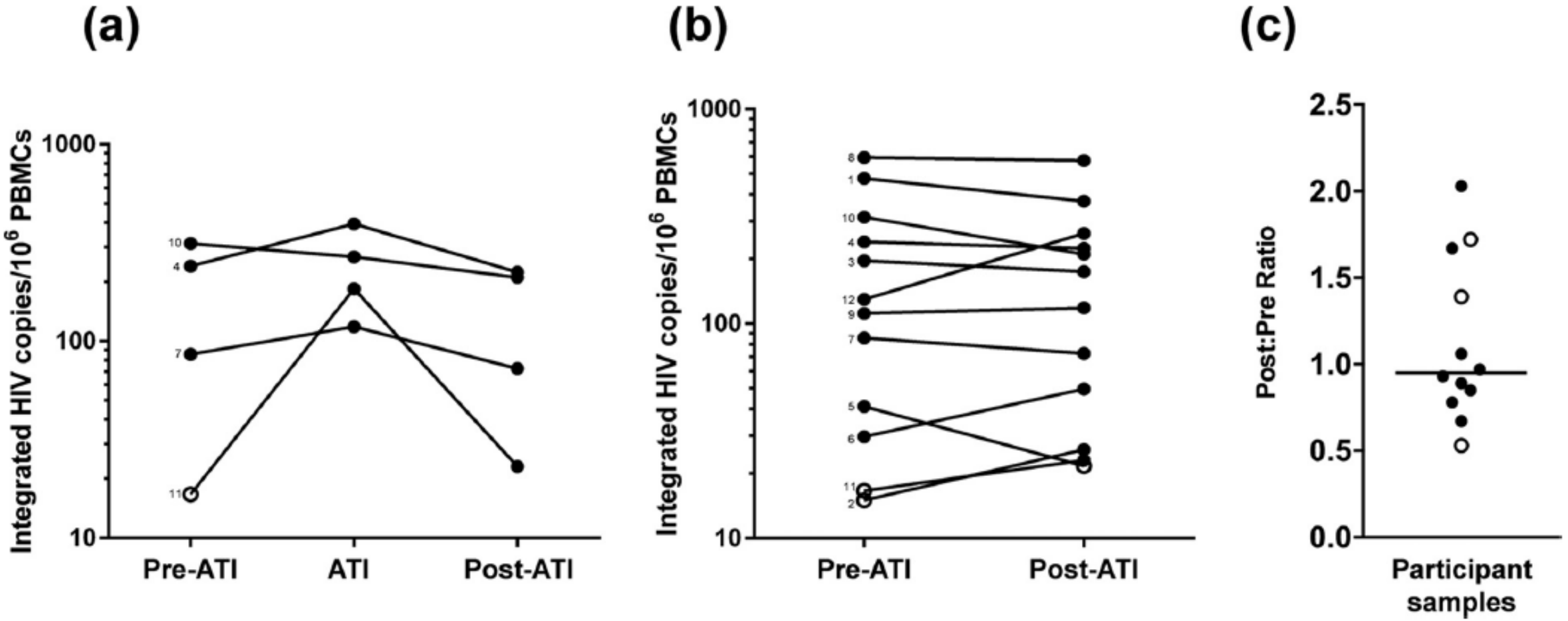


FIG 3 Treatment interruption had minimal effect on levels of integrated HIV DNA in PBMCs. (a) Levels of integrated HIV DNA pre-ATI, during treatment interruption, and post-ATI in four participants. Participant numbers are written next to the corresponding pre-ATI data point. (b) Pre- and post-ATI levels of integrated HIV DNA for 12 participants. For samples that are below the LOD, the LOD for that sample is used (open circle). (c) Ratio of post-ATI to pre-ATI levels of integrated HIV DNA. An open circle represents whether either the pre- or post-ATI time point was below the LOD. The line represents the median value.

No sustained effect of SHORT-term ATI on HIV reservoir

- Minimal change in the levels of integrated HIV-DNA in participants who underwent an ATI, followed by 6 months of ART.

- This suggests that **short-term ATI** can be conducted without a significant impact on the levels of integrated proviral DNA in the peripheral blood.

Strongin Z et al, J Virology 2018; 92(12): e000285

Potential impact of an ATI on the size of the reservoir?

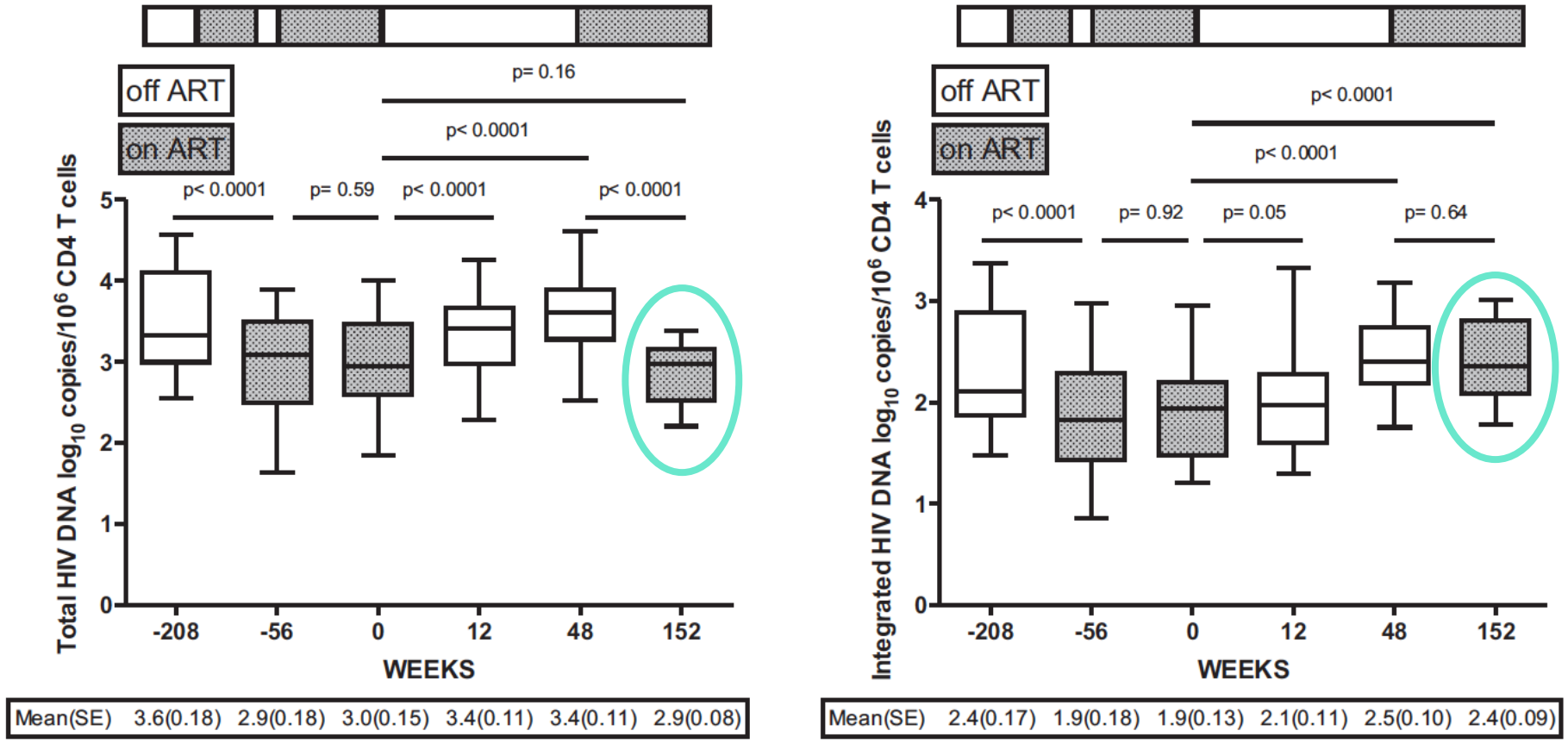


Fig. 1. Dynamics of change of total (left) and integrated (right) HIV-1 DNA during short and long-term periods of analytical therapy interruption and antiretroviral therapy resumption. Box represents the median value and first and third quartiles. The whiskers represent the range (minimum and maximum values). Corrections for multiple comparisons were applied.

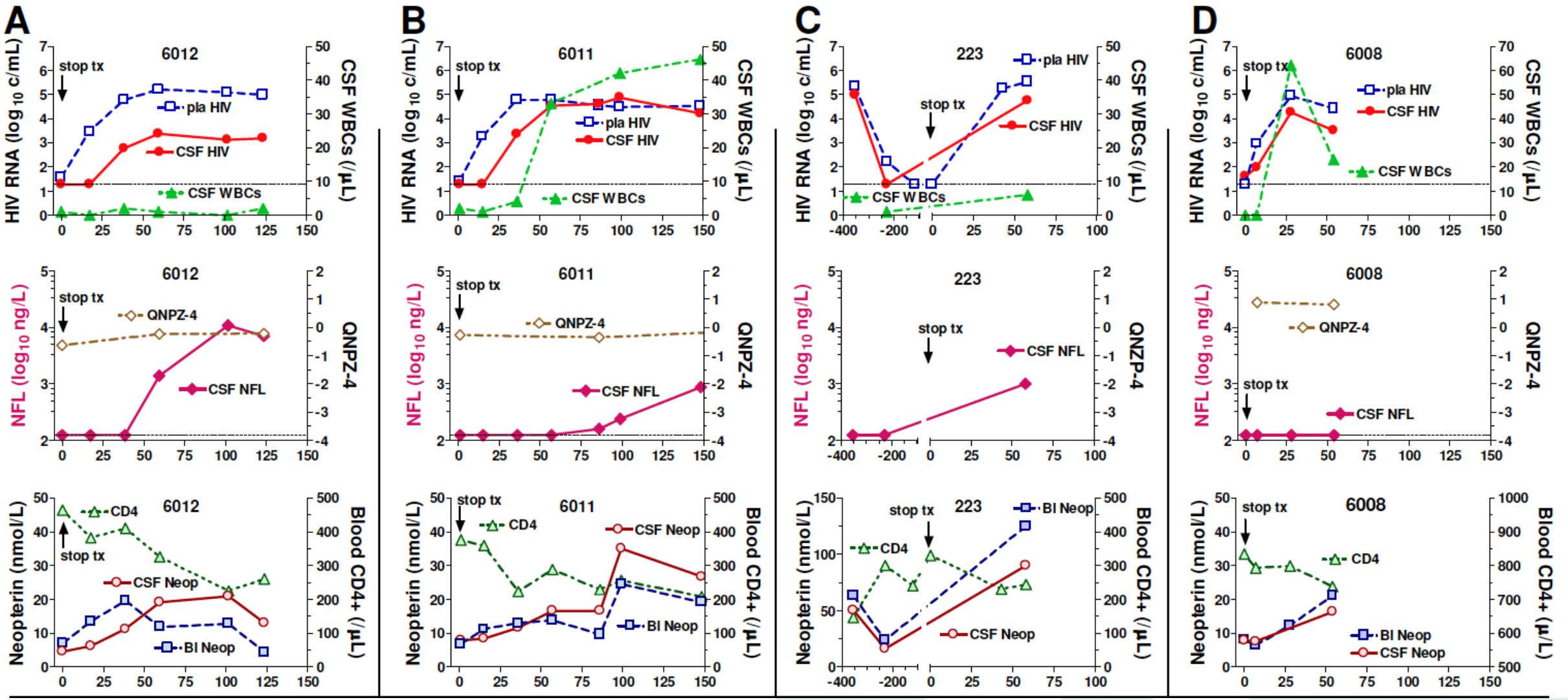
Montserrat M et al, AIDS 2017, 31:1895–1897

Sustained effect of LONG-term ATI on HIV reservoir

- Total HIV-1 DNA increased to pre-ART levels after **48 weeks of ATI** to return to pre-ATI levels after 104 weeks of ART resumption.
- Conversely, integrated HIV-1 DNA remained elevated after ART reinitiation.
- These data suggest that the increase in reservoir after long-term ART discontinuation might not be reversible at midterm

Montserrat M et al, AIDS 2017, 31:1895-1897

ATI and CNS



Gisslén. M et al, AIDS Research and Therapy 2005, 2:6

ATI and CNS

Results: A total of 8 subjects were studied. The median (range) CSF NFL level at baseline was <125 (<125–220) ng/L (normal <250 ng/L). All 8 subjects exhibited an increase in CSF and plasma HIV RNA after stopping therapy, accompanied by intrathecal immunoactivation as evidenced by CSF lymphocytic pleocytosis (7/8 patients) and increased CSF neopterin concentration (5/6 patients). Three subjects showed a consistent increase in CSF NFL, rising from <125 ng/L to a maximum of 880 (at day 148), 1,010 (day 58) and 10,930 ng/L (day 101). None exhibited new neurological symptoms or signs, or experienced functional deterioration during the period off treatment; of 5 who underwent brief quantitative neurological testing, none showed worsening performance.

Conclusion: These findings suggest that resurgence of active HIV replication may result in measurable, albeit subclinical, CNS injury. Further studies are needed to define the frequency and pathobiological importance of the increase in CSF NFL.

Gisslén. M et al, AIDS Research and Therapy 2005, 2:6

Monitoring

- HIV RNA monitoring weekly for 12 weeks, then every other week
- CD4 count monitoring biweekly
- Monitoring of clinical symptoms in particular in people who started ART during “hyperacute” HIV
- Monitoring of participants’ psychosocial experiences

ART restart criteria

- If requested by the participant or their HIV health care provider
- If participant becomes pregnant
- If ART is deemed medically necessary for non-HIV related causes
- Symptomatic HIV disease[9]
- Confirmed absolute CD4 value <350 cells per µL or CD4% <15[10]
- HIV RNA >/= 1,000 copies per mL for 4 weeks[11]
- Absolute HIV RNA >100,000 copies per mL[11]

Julg B et al, Lancet HIV 2019; 6(4): e259-e268

19th EUROPEAN AIDS CONFERENCE
18–21 October 2023
Warsaw, Poland

Potential post treatment HIV controllers have a lower burden of comorbidities and of non-antiretroviral co-medications

M. Ferrara[1], *G. Trevisan*[1], *T. Roatta*[1], *S. Fantino*[1], *V. Maccario*[1], *M. Tettoni*[1], *G. Di Perri*[1], *A. Calcagno*[1], *S. Bonora*[1]

[1]Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

Method: In this monocentric cross-sectional study, we included adult PLWH with PHI and CHI matched according to age, sex, ART duration. We collected immunovirological parameters and comorbidities. We analysed the two groups using Mann-Whitney and Chi-squared test, as appropriate.

Results: 65 PHI and 64 CHI were included. Immunovirological and demographic characteristics of study population are reported in Table 1. No differences were observed in age, sex and ART duration between the groups. In PHI group, higher HIV-RNA zenith ($p<0.001$) and lower CD4 cell count ($p=0.033$) was found compared to CHI group. There was no significant difference in number of ART switch, virological undetectability, prevalence of dual therapy, CD4 count and CD4/CD8 ratio at the last observation.CHI showed to have a higher burden of comorbidities ($p=0.001$), including hypertension ($p=0.012$), psychiatric diseases ($p=0.025$), multimorbidity ($p=0.038$). PHI were significantly less affected by polypharmacy ($p=0.049$). Table 1.

19th EUROPEAN AIDS CONFERENCE
18–21 October 2023
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Potential post treatment HIV controllers have a lower burden of comorbidities and of non-antiretroviral co-medications

M. Ferrara[1], *G. Trevisan*[1], *T. Roatta*[1], *S. Fantino*[1], *V. Maccario*[1], *M. Tettoni*[1], *G. Di Perri*[1], *A. Calcagno*[1], *S. Bonora*[1]

[1]Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

Conclusions: Despite several limitations (including a small sample size), the findings of this study identified clinical differences between PHI and CHI. The significantly lower prevalence of comorbidities in participants in the PHI group is a novel finding that may be explained by a lower level of systemic inflammation and/or a lower HIV reservoires in body tissues. Since no differences were observed in routine immunological and virological biomarkers the identification of potential PCTs requires additional biomarkers (as intact HIV-DNA, HLA phenotypes and immune-activation biomarkers).

Is it possible to define a set of biomarkers that can predict the probability-of-viral-rebound after a potentially successful intervention (i.e., **biomarkers that can predict the likelihood of achieving a PTC phenotype** after ART cessation)?

- **No validated biomarkers predictive of virological control** once cART is stopped
- No validated viral or host biomarker(s) that can predict time to viral rebound or the probability of viral rebound/remission upon ART cessation
- No validated biomarkers of the PTC phenotype
- ATI appear to be necessary until a promising biomarker emerges that robustly predicts post-treatment viral control

Julg B et al, Lancet HIV 2019; 6(4): e259-e268

Giron LB et al, Nature Communications 2022

Parameters that influence HIV reservoir

Several clinical parameters are likely to influence the HIV reservoir size and the association between this reservoir size and TTVR; these include:

- ART regimen
- pre-ART viral load
- time from diagnosis to ART initiation
- ART duration

cART and PPTCs

Highly potent drugs could have a major impact reducing the global level of viral reservoir in blood and tissues

It would be particularly important to test drugs with **high tissue penetration** particularly in lymph nodes where the first steps of viral replication during acute infection are so high

Blips and PTCs

- Using CASCADE data of seroconverters starting ART in PHI (6 months from seroconversion), we estimated proportions experiencing viral blips (400 copies followed by 400 copies HIV-RNA/mL without alteration of regimen) while on ART.
- Loss of control (2 consecutive measurements >1000 copies per milliliter)
- Modified definition of blip as a single plasma HIV-RNA measure >400 copies in a previously suppressed individual followed by subsequent viral suppression without change in ART regimen
- In a sensitivity analysis on blip definitions, we defined additional blip thresholds of HIV-RNA >50, >100, and >200 copies per milliliter.

Fidler S, J Acquir Immune Defic Syndr 2017;74:126-133

TABLE 1. Baseline Characteristics of Individuals Initiating ART Within 6 Months of HIV-1 Seroconversion, Those Subsequently Stopping ART, and Post Treatment Controllers (PTC) in CASCADE

	Started ART	Subsequently Stopped ART	PTC
Total, N	778	228	22
Sex, N (%)			
Male	714 (92)	206 (90)	16 (73)
Female	64 (8)	22 (10)	6 (27)
Risk group			
MSM	581 (75)	167 (73)	10 (45)
MSW	129 (17)	46 (20)	28 (36)
IDU	28 (4)	10 (4)	2 (9)
OTH	40 (5)	5 (2)	2 (9)
ART initiation class, N (%)			
NNRTI	288 (37)	87 (38)	12 (55)
PI	347 (45)	103 (45)	7 (32)
3 N	95 (12)	32 (14)	3 (14)
3 Class	11 (1)	4 (2)	0
Fusion inhibitor	6 (1)	0	0
Integrase inhibitor	30 (4)	2 (1)	0
SC yr, median (IQR)	2004 (2000–2010)	2001 (1999–2005)	2001 (2000–2003)
SC age, yrs, median (IQR)	34 (28–42)	33 (28–41)	35 (28–39)
Time on ART, mo, median (IQR)	16.2 (8.0–35.9)	11.0 (4.2–21.3)	17.4 (6.3–27.6)
Time from SC to ART, mo, median (IQR)	2.3 (0.7–4.1)	2.2 (0.5–3.9)	3.1 (0.6–5.3)
Initial HIV-RNA (log_{10} copies/mL)	5.3 (4.5, 5.9)	5.3 (4.6, 5.9)	4.9 (4.6, 5.6)
# HIV-RNA measurements per year, median (IQR)	3 (1–4)	1 (1–4.2)	3.5 (1–4.0)
HIV-RNA at ART cessation (log_{10} copies/mL), median (IQR)‡	—	0 (0–1.8)	0 (0–1.7)
CD4 at ART initiation	477 (316, 658)	494 (360, 701)	562 (230, 710)
CD4 at ART cessation, median (IQR)	—	709 (519–917)	738 (506–890)
Blips, % (95% CI), % 1 blip, copies/mL			
>50	13 (11 to 16), 78	11 (7 to 18), 87	7 (1 to 44), 0
>100	9 (7 to 12), 85	9 (5 to 16), 85	7 (1 to 42), 100
>200	6 (5 to 9), 79	9 (5 to 15), 77	9 (3 to 43), 100
>400	7 (6 to 9), 84	9 (6 to 14), 89	7 (2 to 36), 100

TABLE 3. Multivariable Analysis of the Factors Associated With Virologic Rebound Among Those Stopping ART Initiated Within 6 Months of HIV Seroconversion Using the CASCADE Dataset

	HR (95% CI)	*P*
Time on ART (per 6-month increase)*	0.84 (0.76 to 0.92)	<0.001
Time from SC to ART (per month increase)†	1.16 (1.04 to 1.28)	0.006
# blips >400 copies/mL (per additional blip)	1.71 (0.94 to 3.10)	0.077
# mean HIV-RNA measurements/year (per additional measurement)	1.10 (1.02 to 1.17)	0.005
HIV-RNA at SC (per $\log_{10}$ increase)‡	1.15 (0.98 to 1.35)	0.086
ART initiation yr (per year increase)	0.91 (0.84 to 0.98)	0.016
Time from ART to viral suppression (per month increase)‡§	0.99 (0.97 to 1.02)	0.93
CD4 at ART initiation (per 100 cells/mm^3 increase)‖	0.99 (0.90 to 1.08)	0.75
CD4 at ART cessation (per 100 cells/mm^3 increase)‖	1.10 (1.01 to 1.20)	0.035
ART class		0.33
NNRTI	1	
PI	0.92 (0.57 to 1.48)	
3 N	1.32 (0.74 to 2.36)	
3 Class	0.24 (0.03 to 1.79)	
Integrase inhibitor	0.77 (0.10 to 6.12)	
SC age	1.00 (0.98 to 1.02)	0.77
Sex		0.49
Male	1	
Female	0.75 (0.33 to 1.69)	
HIV risk group		0.28
MSM	1	
MSW	0.84 (0.44 to 1.58)	
IDU	0.53 (0.14 to 2.03)	
OTH	0.23 (0.03 to 1.73)	

Blips and PTCs

HIV viral blips on therapy are associated with subsequent viral rebound on stopping ART among individuals treated in PHI.

Longer duration on ART is associated with a greater chance of PTC.

Fidler S, J Acquir Immune Defic Syndr 2017;74:126-133

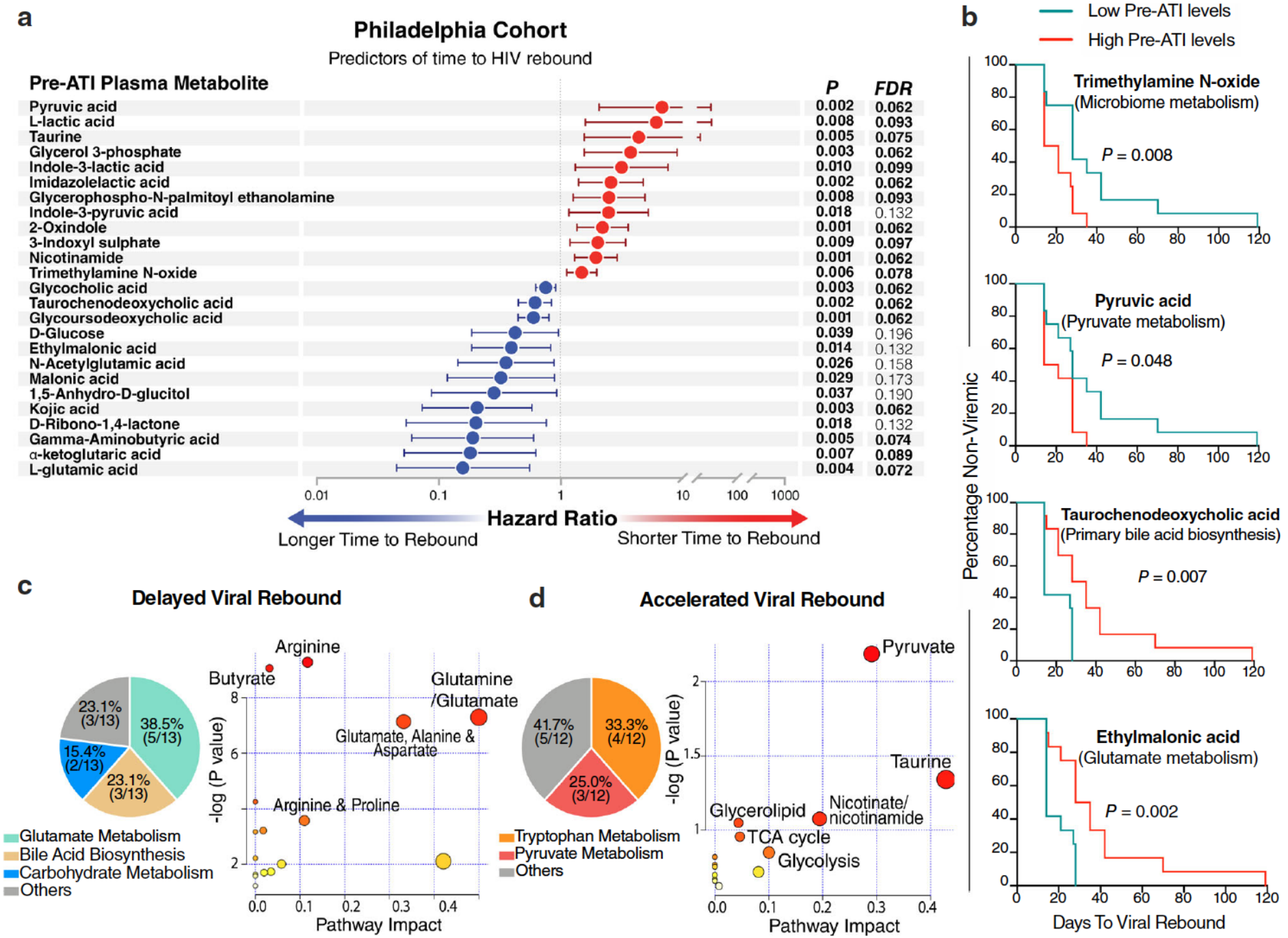
Non invasive plasma glycomic and metabolic biomarkers

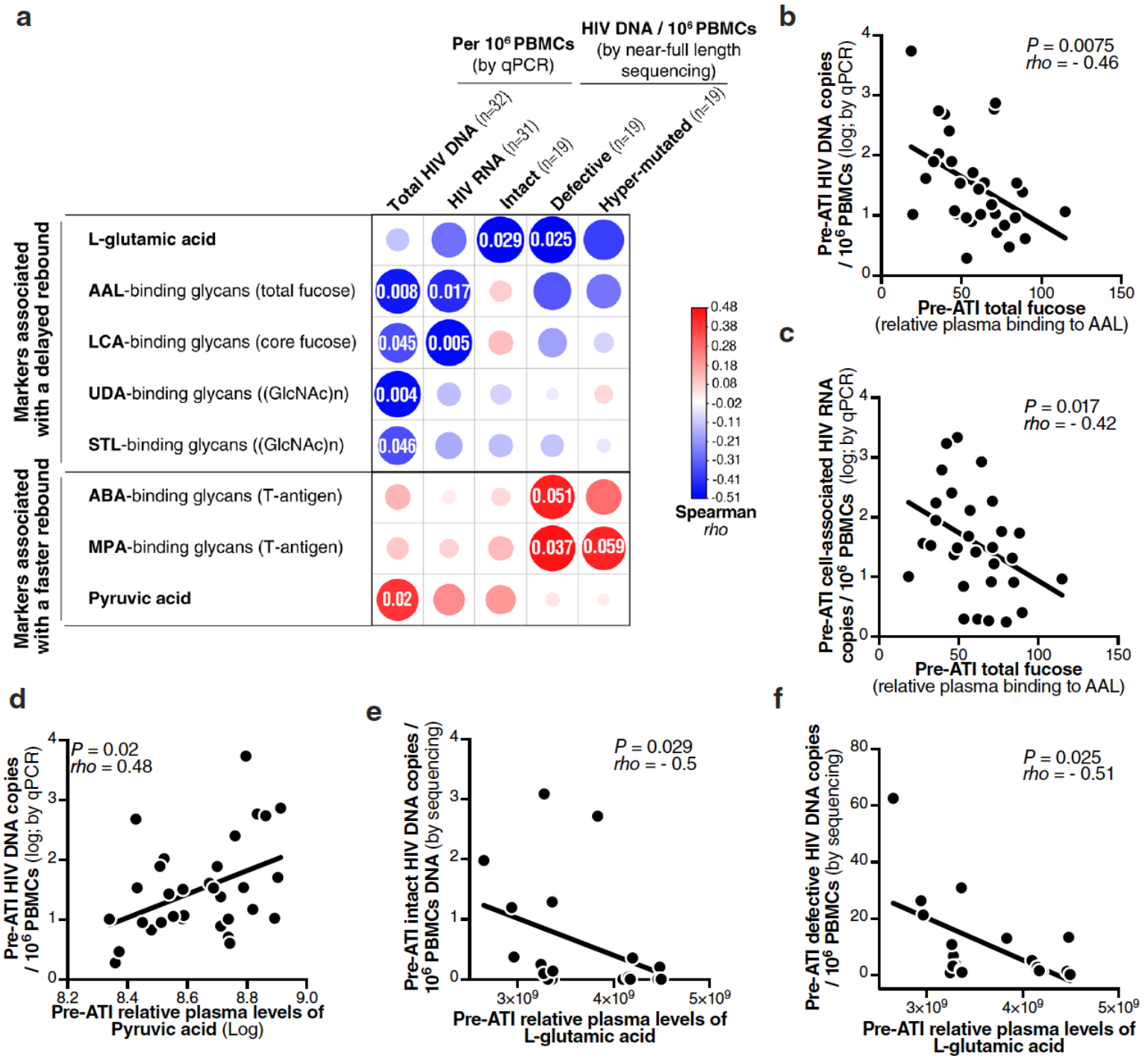
- Plasma glycoproteins and plasma metabolites enter the circulation from tissues through active secretion or leakage.
- Glycomic features in total plasma and on IgG have been identified as biomarkers for inflammatory bowel disease, cancer, and diabetes.
- **Glycans** on circulating glycoproteins have functional significance, as glycans play essential roles in mediating immunological functions, including antibody-dependent cell-mediated cytotoxicity and pro- and anti-inflammatory activities.
- **Plasma metabolites** have been investigated as biomarkers in several diseases (heart disease, Alzheimer's disease, cancer).
- Plasma metabolites are biologically active molecules that can regulate immunological responses, including inflammatory responses

Giron LB et al, Nature Communications 2022

Non invasive plasma glycomic and metabolic biomarkers

- 74 HIV infected, ART-suppressed individuals who underwent ATI (ACTG clinical trials): **27 PTCs**; 47 NCs
- A set of plasma glycans and metabolites were able to predict time-to-viral rebound and probability-of-viral-rebound, even after adjusting for several potential demographic and clinical confounders.
- Using machine-learning models, we combined this set of biomarkers into two multivariate models: a model that predicts time-to-viral-rebound with 74% capacity; and a model that predicts probability-of-viral-rebound with 97.5% capacity.
- Non-invasive plasma biomarkers, with potential functional significance, that predict duration and probability of viral remission after treatment interruption.


a
Philadelphia Cohort
Predictors of time to HIV rebound
Pre-ATI Plasma Metabolite
P
FDR
Pyruvic acid 0.002 0.062
L-lactic acid 0.008 0.093
Taurine 0.005 0.075
Glycerol 3-phosphate 0.003 0.062
Indole-3-lactic acid 0.010 0.099
Imidazolelactic acid 0.002 0.062
Glycerophospho-N-palmitoyl ethanolamine 0.008 0.093
Indole-3-pyruvic acid 0.018 0.132
2-Oxindole 0.001 0.062
3-Indoxyl sulphate 0.009 0.097
Nicotinamide 0.001 0.062
Trimethylamine N-oxide 0.006 0.078
Glycocholic acid 0.003 0.062
Taurochenodeoxycholic acid 0.002 0.062
Glycoursodeoxycholic acid 0.001 0.062
D-Glucose 0.039 0.196
Ethylmalonic acid 0.014 0.132
N-Acetylglutamic acid 0.026 0.158
Malonic acid 0.029 0.173
1,5-Anhydro-D-glucitol 0.037 0.190
Kojic acid 0.003 0.062
D-Ribono-1,4-lactone 0.018 0.132
Gamma-Aminobutyric acid 0.005 0.074
α-ketoglutaric acid 0.007 0.089
L-glutamic acid 0.004 0.072
0.01 0.1 1 10 100 1000
Hazard Ratio
Longer Time to Rebound
Shorter Time to Rebound
b
Low Pre-ATI levels
High Pre-ATI levels
Trimethylamine N-oxide
(Microbiome metabolism)
P = 0.008
Pyruvic acid
(Pyruvate metabolism)
P = 0.048
Taurochenodeoxycholic acid
(Primary bile acid biosynthesis)
P = 0.007
Ethylmalonic acid
(Glutamate metabolism)
P = 0.002
Percentage Non-Viremic
Days To Viral Rebound
c
Delayed Viral Rebound
23.1% (3/13)
38.5% (5/13)
15.4% (2/13)
23.1% (3/13)
Glutamate Metabolism
Bile Acid Biosynthesis
Carbohydrate Metabolism
Others
Arginine
Butyrate
Glutamine /Glutamate
Glutamate, Alanine & Aspartate
Arginine & Proline
-log (P value)
Pathway Impact
d
Accelerated Viral Rebound
41.7% (5/12)
33.3% (4/12)
25.0% (3/12)
Tryptophan Metabolism
Pyruvate Metabolism
Others
Pyruvate
Taurine
Glycerolipid
Nicotinate/ nicotinamide
TCA cycle
Glycolysis
-log (P value)
Pathway Impact


a
Per 10⁶ PBMCs (by qPCR)
HIV DNA / 10⁶ PBMCs (by near-full length sequencing)
Total HIV DNA (n=32)
HIV RNA (n=31)
Intact (n=19)
Defective (n=19)
Hyper-mutated (n=19)
Markers associated with a delayed rebound
L-glutamic acid
AAL-binding glycans (total fucose)
LCA-binding glycans (core fucose)
UDA-binding glycans ((GlcNAc)n)
STL-binding glycans ((GlcNAc)n)
Markers associated with a faster rebound
ABA-binding glycans (T-antigen)
MPA-binding glycans (T-antigen)
Pyruvic acid
0.029
0.025
0.008
0.017
0.045
0.005
0.004
0.046
0.051
0.037
0.059
0.02
0.48
0.38
0.28
0.18
0.08
-0.02
-0.11
-0.21
-0.31
-0.41
-0.51
Spearman rho
b
P = 0.0075
rho = - 0.46
Pre-ATI HIV DNA copies / 10⁶ PBMCs (log; by qPCR)
Pre-ATI total fucose (relative plasma binding to AAL)
c
P = 0.017
rho = - 0.42
Pre-ATI cell-associated HIV RNA copies / 10⁶ PBMCs (log; by qPCR)
Pre-ATI total fucose (relative plasma binding to AAL)
d
P = 0.02
rho = 0.48
Pre-ATI HIV DNA copies / 10⁶ PBMCs (log; by qPCR)
Pre-ATI relative plasma levels of Pyruvic acid (Log)
e
P = 0.029
rho = - 0.5
Pre-ATI intact HIV DNA copies / 10⁶ PBMCs DNA (by sequencing)
Pre-ATI relative plasma levels of L-glutamic acid
f
P = 0.025
rho = - 0.51
Pre-ATI defective HIV DNA copies / 10⁶ PBMCs (by sequencing)
Pre-ATI relative plasma levels of L-glutamic acid

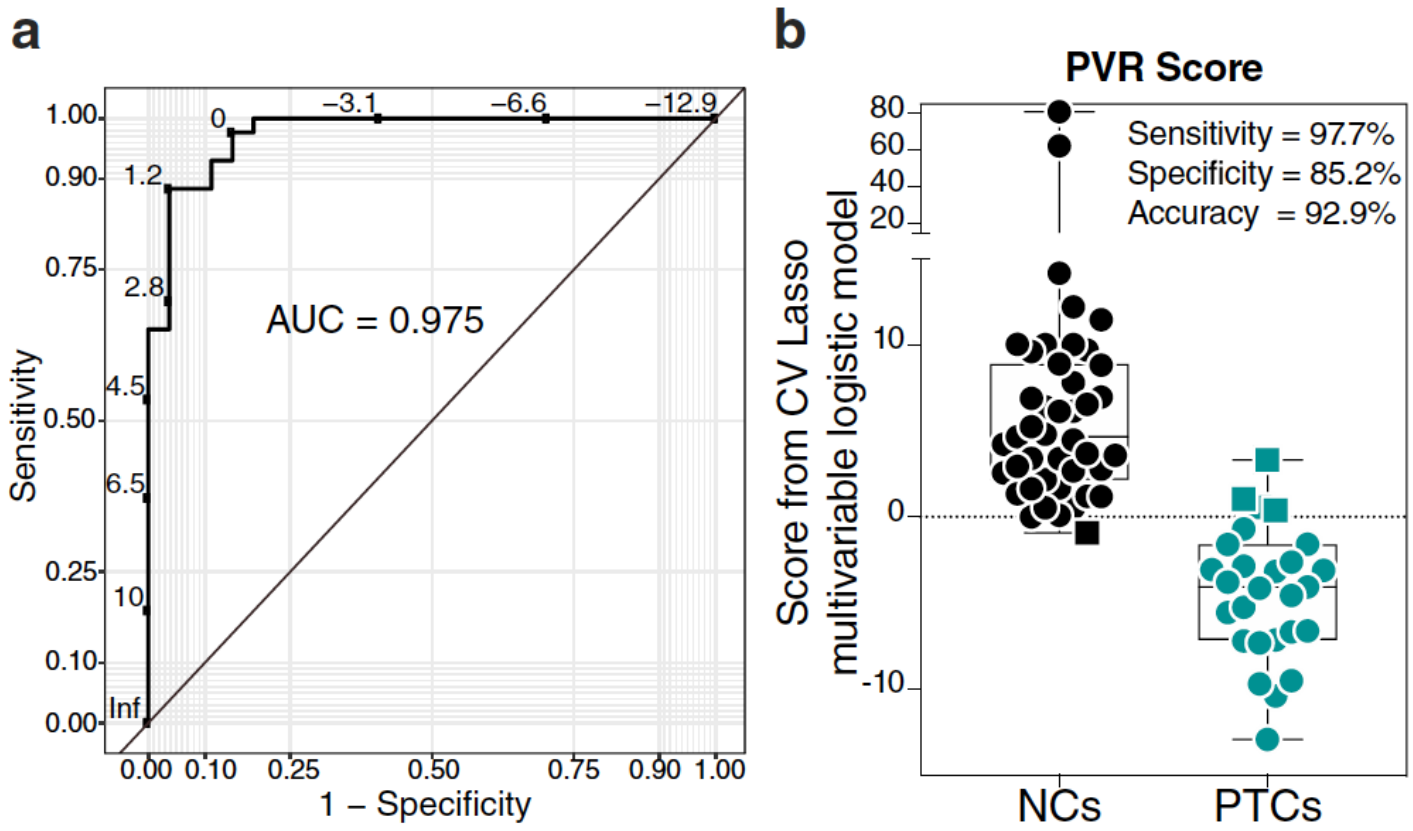
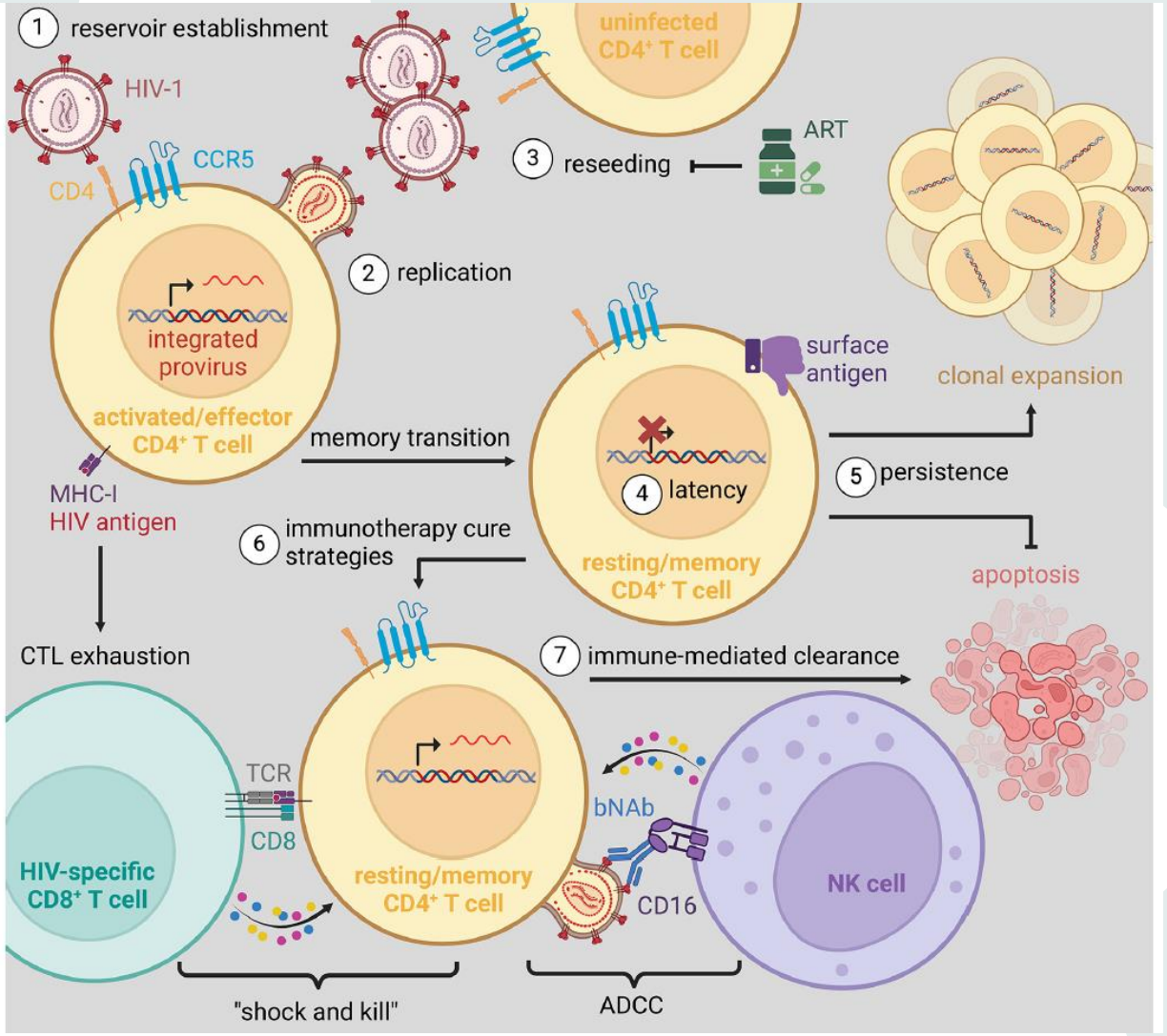
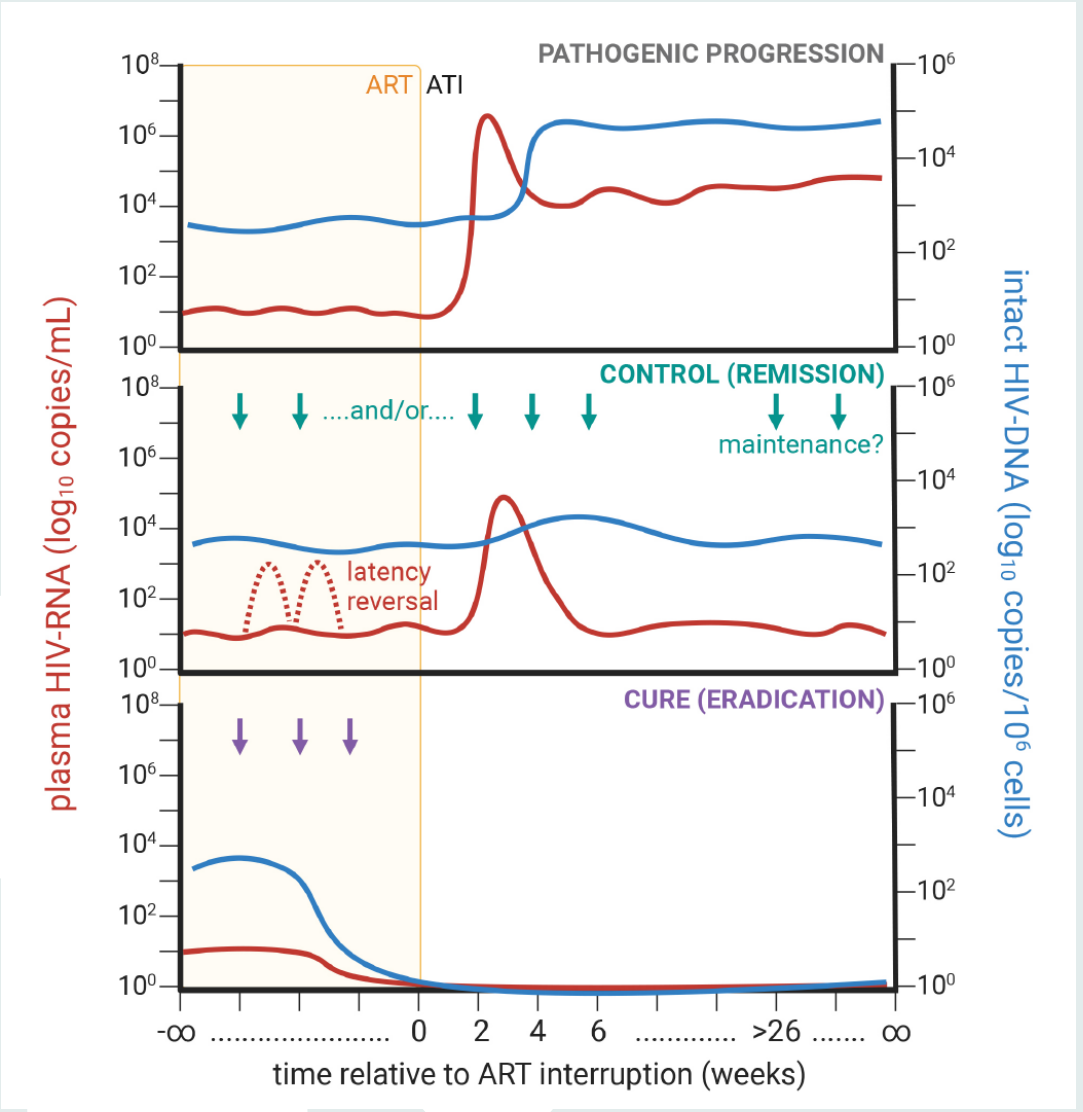


Fig. 7 A multivariable logistic model using Lasso selected variables predicts the probability of viral remission post-ATI. The machine-learning algorithm, Lasso regularization, selected seven markers from the ten markers in Fig. 6. Analysis using this model demonstrates that when these seven markers are combined, their predictive ability is better than the predictive ability of any marker individually (Supplementary Table 9). **a** Receiver operator characteristic (ROC) curve showing the area under the curve (AUC) is 97.5% from the multivariable logistic regression model with seven variables. $n = 70$ biologically independent samples. **b** Coefficients from the multivariable logistic model were used to estimate risk score for each individual and then tested for the ability of these scores to accurately classify post-treatment controllers (PTCs) and non-controllers (NCs) at an optimal cut-point. The model correctly classified 97.7 of NCs (sensitivity), 85.2% of PTCs (specificity) with an overall accuracy of 92.9%. Squares represent individuals the model failed to identify correctly. The center of the box showing median with the whiskers going from each quartile (25th and 75th percentiles) to the minimum and maximum, respectively. $n = 70$ biologically independent samples. PVR probability of viral rebound score. Source data are provided as a Source Data file.

ATI and supplemental intervention





Conclusioni: Potential PTCs

PLWH con follow up di 5/10 anni dalla virosoppressione (VL <50 cp/mL) (AND)

PLWH che hanno iniziato ART nei 12 mesi dalla sieroconversione stimata – entro stadio di Fiebig 6

Conta di CD4+ > 350/500 cells/mmc

Viremie stabilmente <50 cp/ml nei 5/10 anni (AND)

Conclusioni: Potential PTCs

No viral blips/viremia residua nei 5/10 anni (AND)

HIV-DNA <10 copies/10^6 PBMCs (AND)

Bassi livelli di infiammazione (periferica)

Conclusioni

- *Analytical treatment interruptions*: considerazioni etiche
- Strategie complementari a ATI (bNAbs, vaccino terapeutico, immunomodulatori)
- Monitoraggio di HIV-RNA, CD4, CD4/CD8, reservoir virale e monitoraggio clinico

Grazie per l’attenzione

