Clinical risk and therapeutic options of INR

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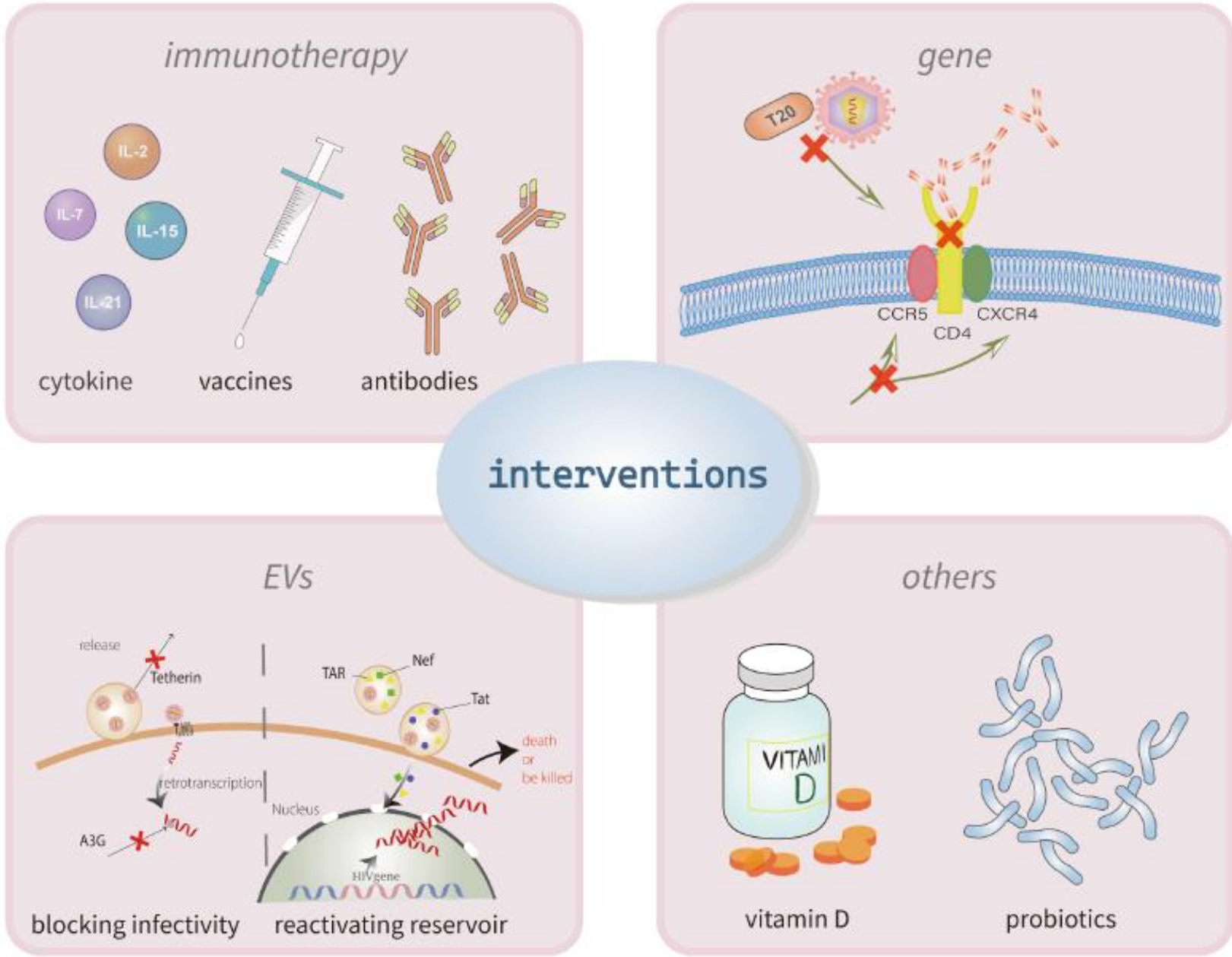
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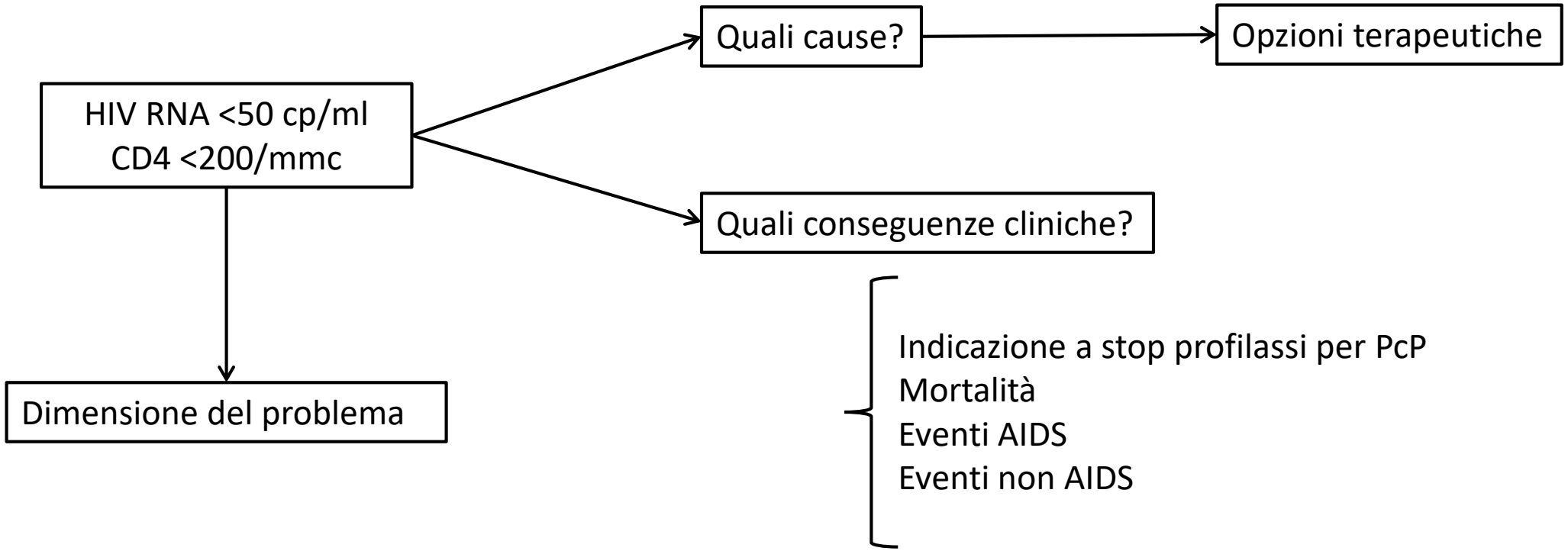
REVIEWED BY

Recent advances in poor HIV immune reconstitution: what will the future look like?

Wenyuan Zhang and Lianguo Ruan*


immunotherapy
IL-2
IL-7
IL-15
IL-21
cytokine
vaccines
antibodies
gene
T20
CCR5
CXCR4
CD4
interventions
EVs
release
Tetherin
TAR
Nef
Tat
death
or
be killed
retrotranscription
Nucleus
A3G
HIVgene
blocking infectivity
reactivating reservoir
others
VITAMI
D
vitamin D
probiotics

La definizione del problema



Sì, ma quanti sono?

TABLE 1 Definitions of INR from the literature and guideline.

Definition of INRs	References
Increase in the CD4⁺ T cell count <200 cells/μl from baseline at 2 years after cART initiation, with an undetectable plasma VL	García et al. (2019)
Total CD4⁺ T cell counts <200 cells/μl at 2 years after cART initiation, with an undetectable plasma VL	Xie et al. (2021)
Total CD4⁺ T cell count <350 cells/μl 2 years after cART initiation, with an undetectable plasma VL	Dai et al. (2021), Rousseau et al. (2021), Shive et al. (2021)
Total CD4⁺ T cell count <350 cells/μl 2 years after cART initiation, with plasma HIV-1 RNA < 50 copies/ml	Geng et al. (2021), Malazogu et al. (2021), Vlasova et al. (2021)
Total CD4⁺ T cell count <350 cells/μl 2 years after cART initiation, with plasma HIV-1 RNA < 50 copies/ml at least 12 months	Bandera et al. (2018)
Total CD4⁺ T cell counts <350 cells/μl 8 years after cART initiation, with an undetectable plasma VL	Luo et al. (2022)
Increase in the CD4⁺ T cell count <20% from baseline at 1 year after cART initiation, with an undetectable plasma VL	Lv et al. (2021)
CD4/CD8 ratio < 1 at 24 weeks after cART initiation, with plasma HIV-1 RNA < 50 copies/ml	Russo et al. (2022)

VL, viral load.

Zhang et al, Frontiers in Microbiol 2023

Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease

Christophe Piketty, Philippe Castiel, Laurent Belec*, Dominique Batisse, Ali Si Mohamed*, Jacques Gilquin, Gustavo Gonzalez-Canali, Didier Jayle, Marina Karmochkine, Laurence Weiss, Jean Pierre Aboulker† and Michel D. Kazatchkine

AIDS 1998, **12**:745–750

Table 2. Proportion of responder and non-responder patients to triple combination antiretroviral therapy (n = 162).

		Follow-up (months)	
	No. patients (%)	Mean ± SE	Median (range)
Immunological and virological responders*	92 (56.8)	12.1 ± 0.3	12.6 (2.1–15.4)
Patients who exhibited no immunological or virological response	8 (4.9)	7.6 ± 1.5	8.2 (1.4–13.0)
Patients who exhibited an immunological response and failed to exhibit a virological response	17 (10.5)	10.1 ± 1.0	10.4 (1.2–15.2)
Patients who exhibited a virological response and failed to exhibit an immunological response	17 (10.5)	6.6 ± 1.0	5.5 (1.2–13.5)
Patients who exhibited a transient virological response followed by a failure to respond to therapy	20 (12.3)	11.1 ± 0.5	11.7 (5.8–13.8)
Not assessed†	8 (5)		

*An immunological response to therapy was defined as an increase in the number of CD4 cells $> 50 \times 10^6$/l above baseline throughout the period of follow-up; a virological response was defined as a decrease in plasma viral load > 1 $\log_{10}$ copies/ml compared with baseline or achievement of undetectable plasma HIV RNA levels throughout the period of follow-up. †Five patients died within the first month of treatment; three patients were lost to follow-up after 1 month.

Piketty et al, AIDS 1998

Southern African Journal of HIV Medicine
ISSN: (Online) 2078-6751, (Print) 1608-9693

CD4 testing after initiation of antiretroviral therapy: Analysis of routine data from the South African HIV programme

Lilian RR et al., South Afr J HIV Med. 2020

TABLE 1: Characteristics of immunological non-responders (CD4 count ≤ 350 cells/mm³) compared with immunological responders (CD4 count > 350 cells/mm³) amongst patients with a suppressed viral load who had been on ART for more than 4 years

Variables	Immunological non-responder, *n* = 18 556		Immunological responder, *n* = 74 134		Unadjusted OR		Adjusted OR†	
	n	%	*n*	%	OR (95% CI)	*p*-value	OR (95% CI)	*p*
Last ART regimen								
First line	13 615	18.3	60 709	81.7	Ref		Ref	
Second line	2208	29.5	5282	70.5	**1.85 (1.76–1.96)**	**< 0.001**	**1.79 (1.68–1.91)**	**< 0.001**
Third line	34	26.6	94	73.4	**1.54 (1.04–2.28)**	**0.031**	1.41 (0.85–2.35)	0.188
Unassigned	22	22.5	76	77.6	1.22 (0.76–1.97)	0.403	0.83 (0.44–1.59)	0.581
Age at ART start, years								
15–25	1104	15.4	6073	84.6	Ref		Ref	
25–35	5836	16.9	28 748	83.1	**1.12 (1.04–1.20)**	**0.001**	0.99 (0.90–1.09)	0.886
35–45	6662	21.1	24 851	78.9	**1.49 (1.39–1.60)**	**< 0.001**	**1.15 (1.05–1.27)**	**0.003**
≥ 45	4954	25.5	14 462	74.5	**1.93 (1.80–2.08)**	**< 0.001**	**1.50 (1.37–1.66)**	**< 0.001**
Gender								
Female	9902	15.3	54 749	84.7	Ref		Ref	
Male	8654	30.9	19 385	69.1	**2.45 (2.37–2.53)**	**< 0.001**	**2.28 (2.19–2.38)**	**< 0.001**
Baseline CD4, cells/mm³								
≤ 350	13 831	21.6	50 266	78.4	Ref		Ref	
> 350	664	8.0	7669	92.0	**0.32 (0.29–0.34)**	**< 0.001**	**0.35 (0.32–0.38)**	**< 0.001**
TB status								
None/unknown	18 393	19.9	73 955	80.1	Ref		Ref	
Confirmed TB	163	47.7	179	52.3	**3.57 (2.88–4.42)**	**< 0.001**	**2.49 (1.81–3.43)**	**< 0.001**

Lilian et al., South Afr J HIV Med. 2020

Sì ma quali sono le conseguenze?

Pneumocystis jiroveci pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/μl when viral replication is suppressed

Gianni E. D'Egidio[a], Stephen Kravcik[a,b,c], Curtis L. Cooper[a,c], D. William Cameron[a,b,c], Dean A. Fergusson[a,b] and Jonathan B. Angel[a,b,c]

AIDS 2007, **21**:1711–1715

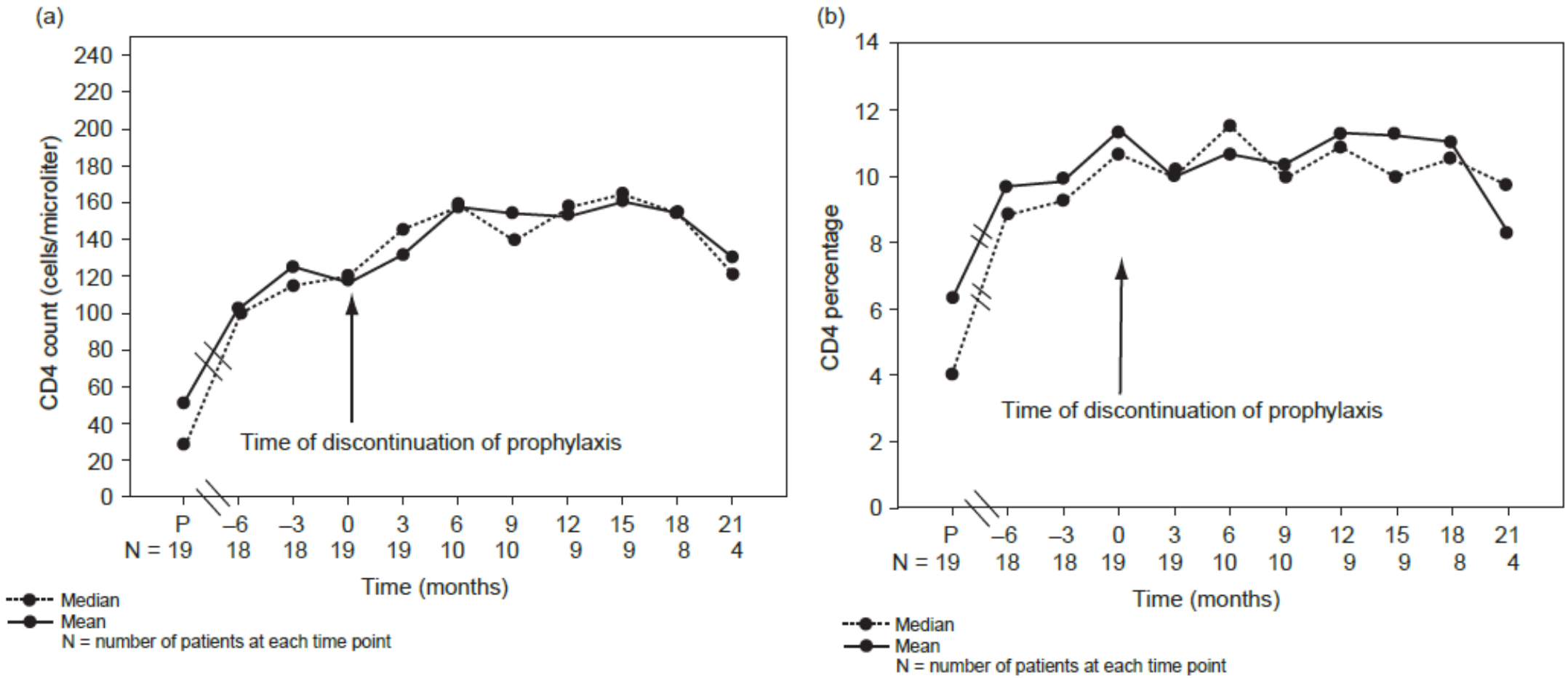


Fig. 1. Mean and median CD4+ T-cell count (cells/μl) (a) and mean and median CD4+ percentage (b) over time in months. P = pre-antiretroviral therapy. Six and 3 month time points before cessation of prophylaxis were included. The cessation of prophylaxis is indicated by time zero.

Is It Safe to Discontinue Primary *Pneumocystis jiroveci* Pneumonia Prophylaxis in Patients with Virologically Suppressed HIV Infection and a CD4 Cell Count <200 Cells/μL?

The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE)

Clinical Infectious Diseases 2010;51(5):611–619

Table 3. Incidence of Primary *Pneumocystis jiroveci* Pneumonia (PcP) after Cessation of PcP Prophylaxis following Initiation of Combination Antiretroviral Therapy (cART)

Variable				No. of PYFU	No. of events	Incidence rate per 1000 PYFU (95% CI)
CD4 cell count, cells/μL	cART	Viral load, copies/mL	PcP prophylaxis			
≤100	"On" or "off"	Any	"On" or "off"	666.9	17	25.5 (14.9–40.8)
≤100	"On"	Any	"On" or "off"	493.7	7	14.2 (5.7–29.2)
≤100	"On"	<400	"On" or "off"	282.4	4	14.2 (3.9–36.3)
≤100	"On"	<400	"Off"	104.2	4	38.4 (10.5–98.3)
101–200	"On" or "off"	Any	"On" or "off"	1578.4	2	1.3 (0.2–4.6)
101–200	"On"	Any	"On" or "off"	1362.9	0	0 (0–2.7)
101–200	"On"	<400	"On" or "off"	1070.5	0	0 (0–3.5)
101–200	"On"	<400	"Off"	570.4	0	0 (0–6.5)
>200	"On" or "off"	Any	"On" or "off"	15,915.2	5	0.3 (0.1–0.7)
>200	"On"	Any	"On" or "off"	15,182.9	1	0.1 (0.002–0.4)
>200	"On"	<400	"On" or "off"	14,604.3	1	0.1 (0.002–0.4)
>200	"On"	<400	"Off"	13,269.4	0	0 (0–0.3)

For primary PcP, a total of 24 events occurred during 18,160.5 person-years of follow-up (PYFU), for an incidence of 1.3 cases per 1000 PYFU. All strata are time updated (ie, they are current values). CI, confidence interval.

Clinical Infectious Diseases

MAJOR ARTICLE

Withholding Primary Pneumocystis Pneumonia Prophylaxis in Virologically Suppressed Patients With Human Immunodeficiency Virus: An Emulation of a Pragmatic Trial in COHERE

Andrew Atkinson,[1,2] Marcel Zwahlen,[3] Diana Barger,[4] Antonella d'Arminio Monforte,[5] Stephane De Wit,[6] Jade Ghosn,[7,8] Enrico Girardi,[9] Veronica Svedhem,[10,11] Philippe Morlat,[4,12] Cristina Mussini,[13] Antoni Noguera-Julian,[14,15,16,17] Christoph Stephan,[18] Giota Touloumi,[19] Ole Kirk,[20] Amanda Mocroft,[21] Peter Reiss,[22,23] Jose M. Miro,[24] James R. Carpenter,[2,25] and Hansjakob Furrer[1]; for the Opportunistic Infections Project Working Group of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

domized trial. Patients taking PcP prophylaxis were eligible for the emulated trial if their CD4 count was ≤200 cells/μL in line with existing recommendations. We compared the following 2 strategies for stopping prophylaxis: (1) when CD4 count was >200 cells/μL for >3 months or (2) when the patient was virologically suppressed (2 consecutive HIV RNA ≤400 copies/mL). Patients were ar-

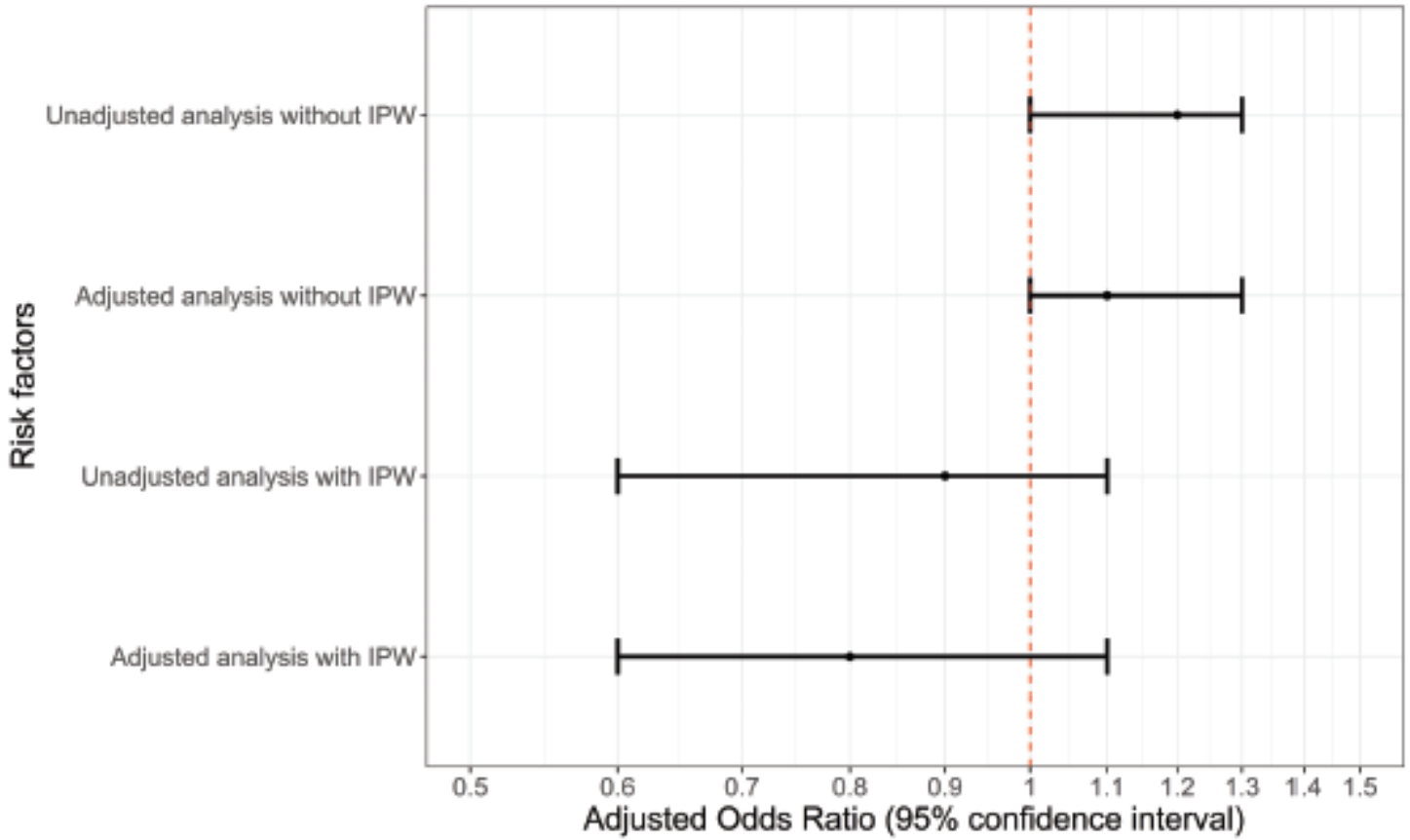


Figure 1. Hazard ratio estimates and 95% confidence intervals from the fitted unadjusted and adjusted models with and without IPW; hazard ratios <1 indicate that the new strategy using viral suppression as a criterion reduces risk compared with the existing strategy based on CD4 count. Abbreviation: IPW, inverse probability weighting.

Atkinson et al (COHERE), Clin Infect Dis 2021

Conseguenze cliniche di INR

- Prolungare profilassi per PcP? ☒ No

Journal of Medical Virology 76:153–160 (2005)

Clinical Outcome After 4 Years Follow-Up of HIV-Seropositive Subjects With Incomplete Virologic or Immunologic Response to HAART

Emanuele Nicastri,[2] Antonio Chiesi,[3] Claudio Angeletti,[2] Loredana Sarmati,[1] Lucia Palmisano,[3] Andrea Geraci,[3] Massimo Andreoni,[1]* Stefano Vella,[3] and Italian Antiretroviral Treatment Group (IATG)

[1]*Department of Public Health, University of Rome Tor Vergata, Rome, Italy*
[2]*National Institute of Infectious Diseases, IRCCS L. Spallanzani, Rome, Italy*
[3]*Department of Drug Research and Evaluation, Istituto Superiore di Sanità, Rome, Italy*

TABLE IV. Hazard Ratios of Progression to a New ADI or Death According to Viro-Immunologic Response After 12 Months of Treatment and Baseline Characteristics

	Progression to new ADI or death		
	OR[a]	95% CI	*P*
Response after 12 months of treatment			
Complete response	1.00		
Immunologic only response	2.32	1.36–3.95	0.002
Virologic only response	1.94	1.06–3.52	0.030
No response	6.07	3.86–9.55	<0.001

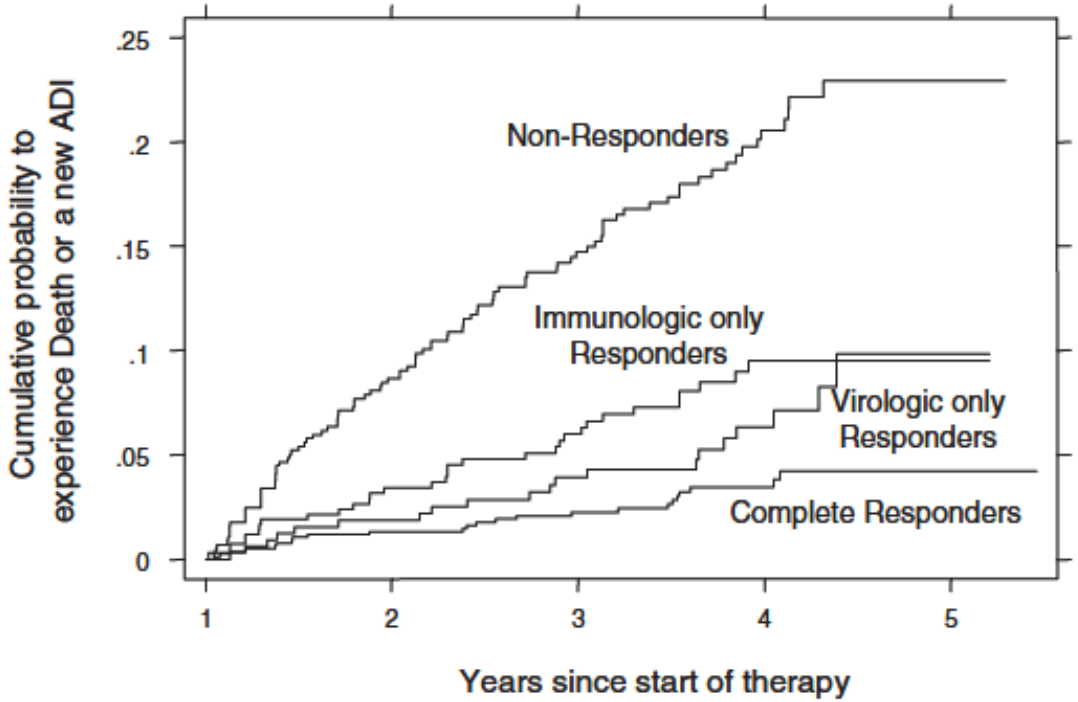


Fig. 1. Kaplan–Meier estimates of cumulative probability to experience death or a new AIDS defining illness (AID) according to the response at month 12 since the start of therapy.

Nicastri et al., J Med Virol 2005

Engsig *et al. BMC Infectious Diseases* 2010, **10**:318
http://www.biomedcentral.com/1471-2334/10/318

BMC
Infectious Diseases

RESEARCH ARTICLE Open Access

Long-term mortality in HIV patients virally suppressed for more than three years with incomplete CD4 recovery: A cohort study

Frederik N Engsig[1*], Jan Gerstoft[1], Gitte Kronborg[2], Carsten S Larsen[3], Gitte Pedersen[4], Birgit Røge[5], Janne Jensen[6], Lars N Nielsen[7], Niels Obel[1]

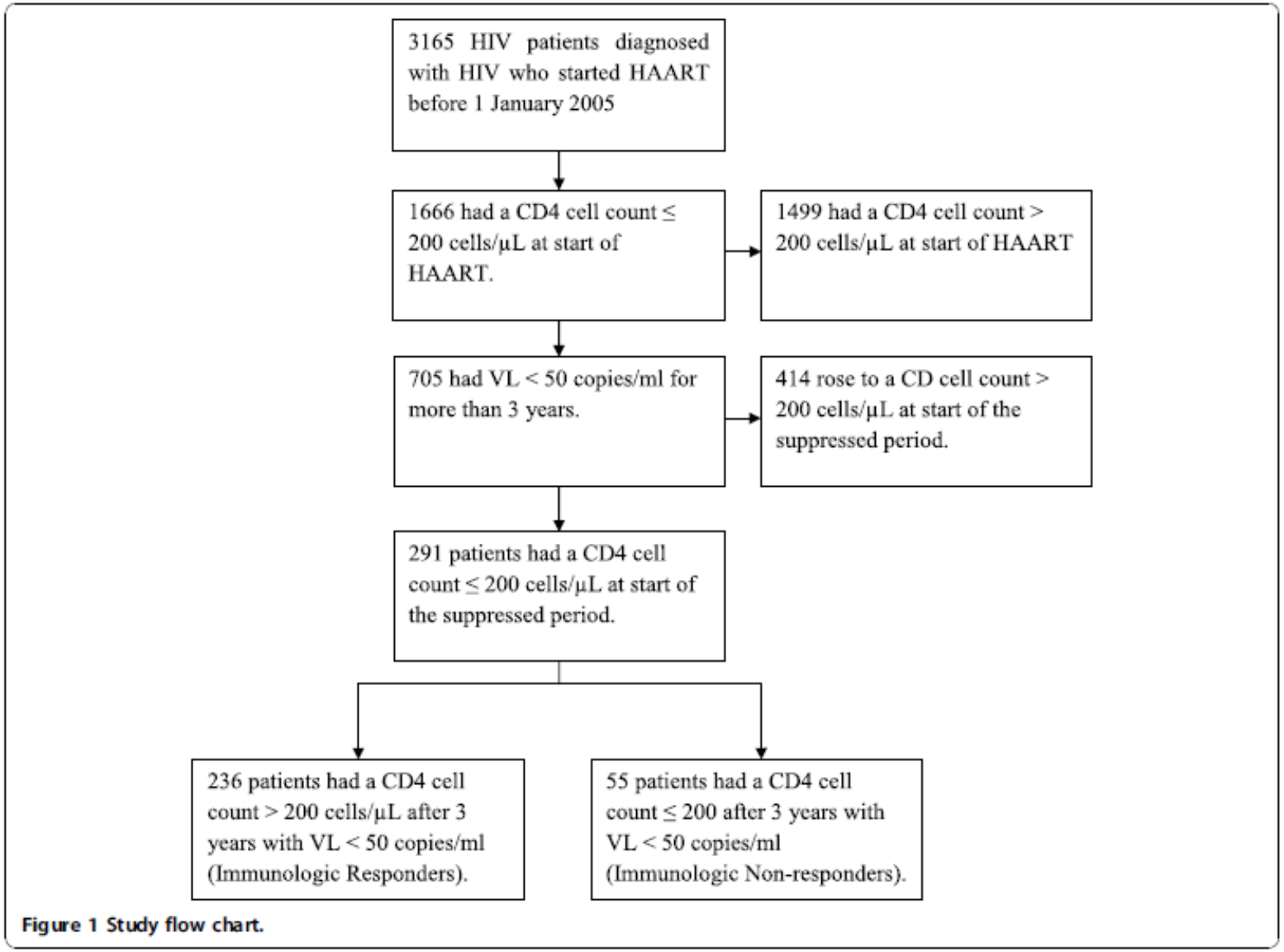


Figure 1 Study flow chart.

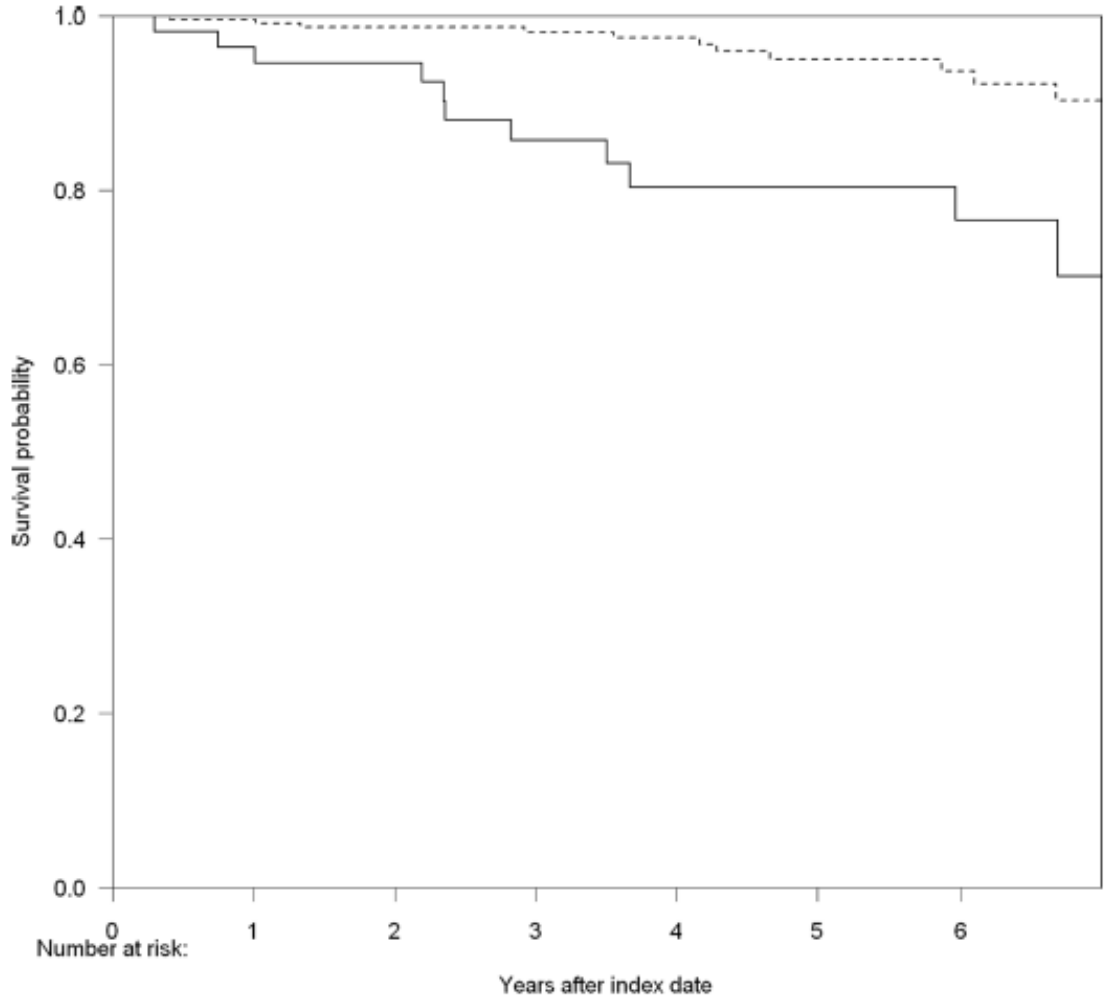


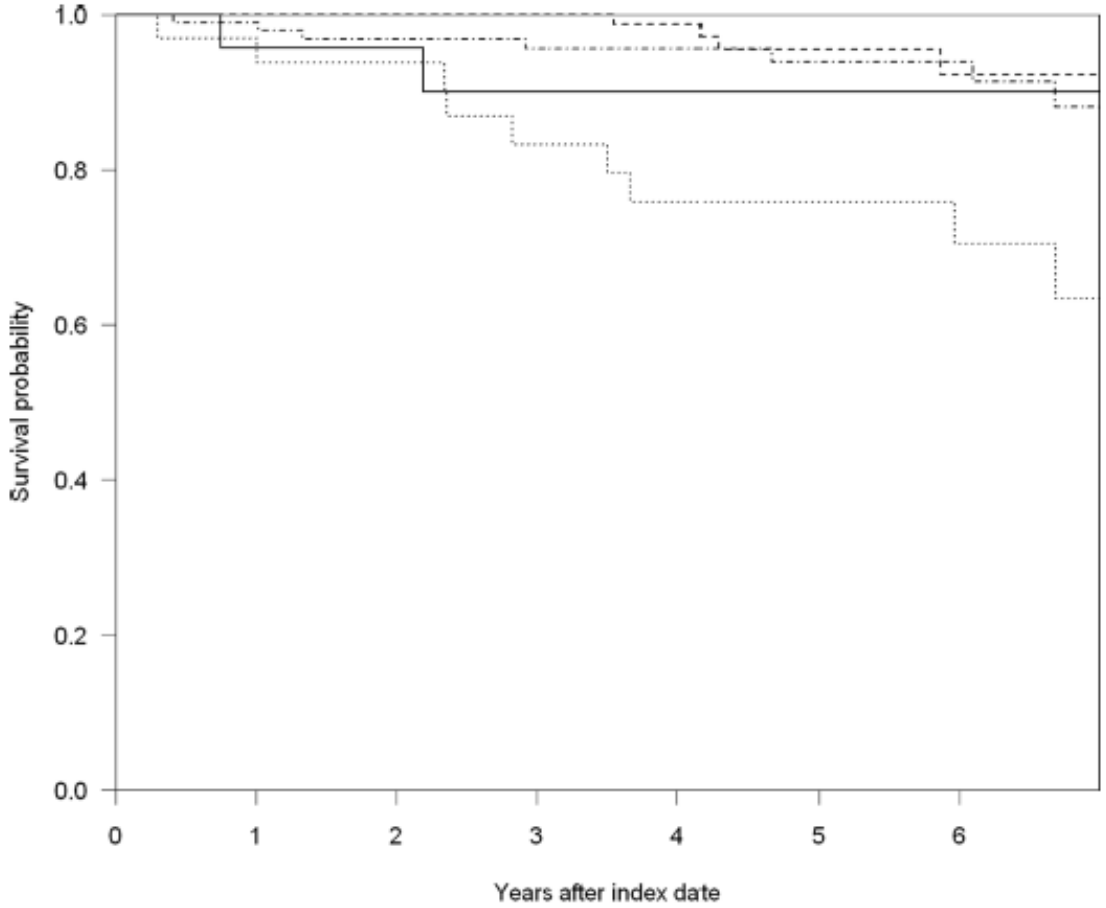
Figure 2 Kaplan-Meier curves for overall survival according to immunologic response at index date: 1. CD4 cell count ≥ 200 cells/μL (broken line), 2. CD4 cell count < 200 cells/μL (full line). Index date was defined at the date of first CD4 measurement after three years of viral suppression (VL < 50 HIV-RNA copies/ml).

Table 2 Odds ratios (OR) for immunological non-response in patients on successful HAART for more than three years

Characteristics	OR Un-adjusted (95% CI*)	OR, Adjusted ** (95% CI)
Male gender	2.18 (0.94 - 5.09)	1.73 (0.73 - 4.14)
More than 40 years old at index date	2.53 (1.390 - 4.63)	2.32 (1.25 - 4.29)
Caucasians	2.23 (1.01 - 4.98)	1.09 (0.36 - 3.36)
Route of HIV infection		
Men who have sex with men	1.0	
Heterosexually infected	0.48 (0.24 - 0.96)	0.73 (0.30 - 1.78)
Injection drug user	1.67 (0.63 - 4.54)	3.06 (0.98 - 9.52)
Other	0.62 (0.22 - 1.75)	0.63 (0.20 - 1.96)
Chronic HCV infection	1.84 (0.76 - 4.43)	2.11 (0.79 - 5.61)
Cancer within 13 years prior to index date	1.72 (0.78 - 3.81)	1.47 (0.63 - 3.44)
One or more AIDS defining events prior to index date	0.83 (0.46 - 1.50)	0.84 (0.46 - 1.53)
Diagnosed with HIV before 1 January 1995	1.46 (0.81 - 2.63)	1.43 (0.72 - 2.86)
Nadir CD4 cell count less than 50 cells/μL	1.59 (0.86 - 2.96)	1.06 (0.43 - 1.75)
More than one year from first CD4 ≤ 200 cells/μL to start of the virologically suppressed period	2.03 (1.12 - 3.68)	2.28 (1.18 - 4.43)

*Confidence interval (95%CI).

**All estimates adjusted for age and gender.



Number at risk:

1.	23	17	9	7
2.	140	107	64	26
3.	32	27	20	13
4.	96	85	69	39

Figure 3 Kaplan-Meier curves for overall survival according to CD4 count at index date and stratified by time from first CD4 cell count < 200 cells/μL to start of the virally suppressed period: 1) CD4 ≥ 200 cells/μL and ≤ one year (full line), 2) CD4 ≥ 200 cells/μL and > one year (bar line). 3) CD4 < 200 cells/μL and ≤ one year (dot and bar line). 4) CD4 < 200 cells/μL and > one year (dot line).

We only encountered two AIDS related deaths suggesting that these are rare after prolonged HAART even without adequate CD4 recovery. Thus, it seems that the INRs are not immune-suppressed in the classical sense where a low CD4 count leads to AIDS defining diseases and eventually death. Still, we cannot rule out that there is a biological cause of the increased mortality in immunological non-responders related to immunodeficiency and that our study simply do not have power enough to demonstrate an association.

The risk factors for incomplete CD4 cell recovery and increased mortality points toward earlier diagnosis of HIV as the main prophylactic measure. Also, the increased mortality in these patients calls for increased concern in terms of treatment and screening for co-morbidity.

We conclude that age and prolonged immunological suppression are risk factors for incomplete CD4 cell recovery in patients with otherwise successful HAART. Patients with insufficient immunological response have substantially increased long-term mortality compared to IRs, but the increased mortality is mainly associated with prolonged immunological suppression prior to VL suppression and IDU. We therefore presume that in the modern HAART era where patients are started early on HAART the prevalence of insufficient CD4 recovery will decrease substantially.

Risk of clinical progression among patients with immunological nonresponse despite virological suppression after combination antiretroviral treatment

Giuseppe Lapadula[a], Alessandro Cozzi-Lepri[b], Giulia Marchetti[d], Andrea Antinori[c], Alessandro Chiodera[e], Emanuele Nicastri[c], Giustino Parruti[f], Massimo Galli[g], Andrea Gori[a], Antonella d'Arminio Monforte[d], for the ICONA Foundation Study

AIDS 2013, **27**:769–779

Nonetheless, in the unadjusted analysis the incidence rates among INR [4.41 (95% CI 3.38–5.74) events per 100 PYFU] were significantly higher than among immunological responders [1.84 (95% CI 1.58–2.14) events per 100 PYFU], with a crude ratio of 2.39 (95% CI 1.77–3.25; $P < 0.001$). Immunological nonresponse was confirmed to be an independent predictor of clinical progression (adjusted rate ratio 2.93; 95% CI 2.06–4.16, $P < 0.001$) in a multivariable model adjusted for baseline characteristics of the patients (age, sex, nationality, mode of HIV transmission, previous AIDS diagnosis, baseline hepatitis coinfection status, calendar year of starting cART, CD4 cell count, CD8 cell count and viral load at starting cART and class of cART started). Interestingly, INR remained independently associated with a higher risk of risk of developing the defined outcome also after adjustment for current $CD4^+$ T-cell count (adjusted rate ratio 1.94; 95% CI 1.39–2.72, $P < 0.001$, Table 3)

INR definiti come mancato incremento di CD4 di almeno il 20%

Lapadula et al, AIDS 2013

RESEARCH ARTICLE

Risk of Severe Non AIDS Events Is Increased among Patients Unable to Increase their CD4 + T-Cell Counts >200+/μl Despite Effective HAART

Giuseppe Lapadula[1]*, Liliane Chatenoud[2], Andrea Gori[1], Francesco Castelli[3], Simona Di Giambenedetto[4], Massimiliano Fabbiani[4], Franco Maggiolo[5], Emanuele Focà[3], Nicoletta Ladisa[6], Laura Sighinolfi[7], Massimo Di Pietro[8], Angelo Pan[9], Carlo Torti[3,10], Italian MASTER Cohort[¶]

Lapadula et al, Plos One 2015

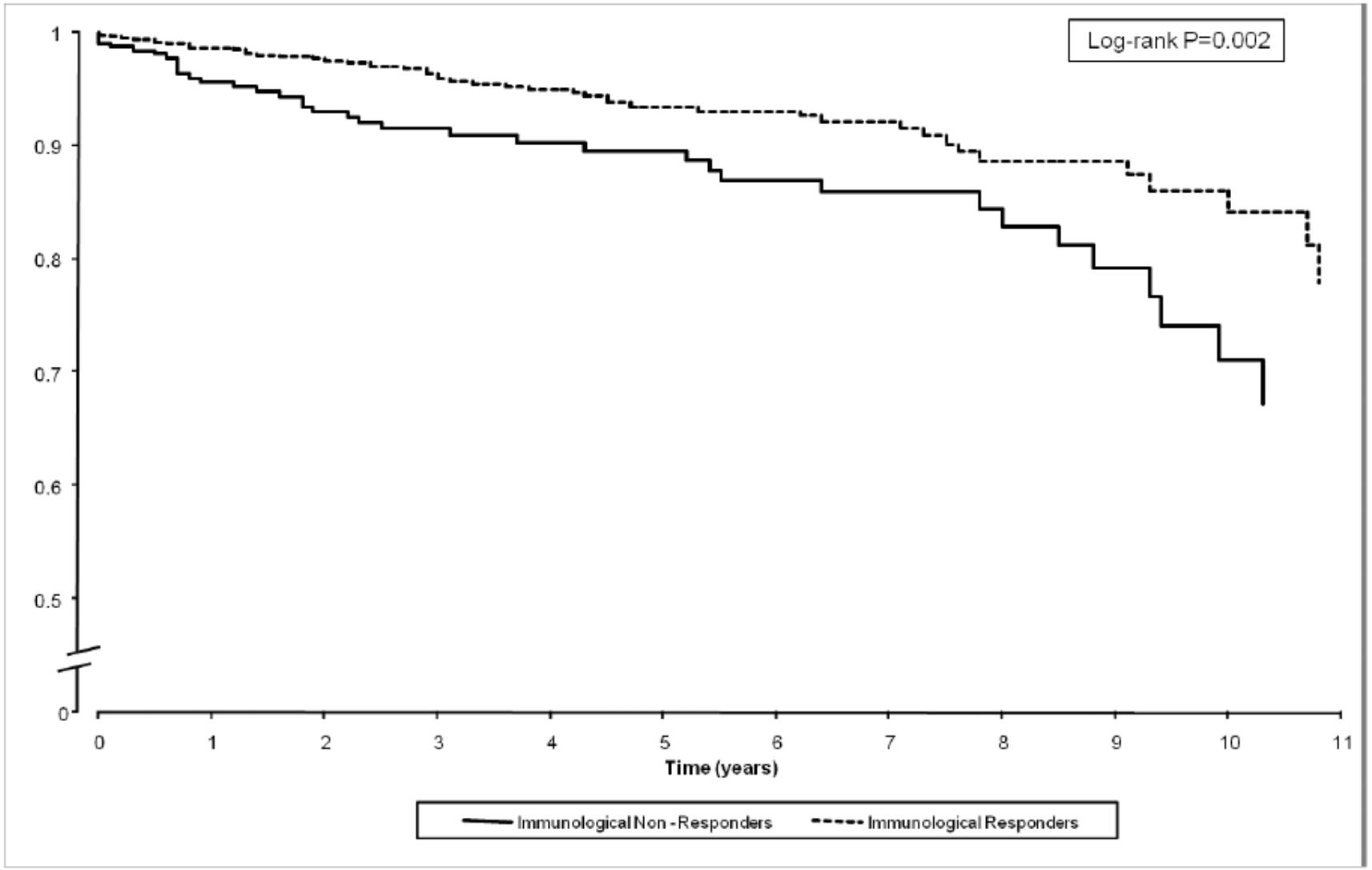


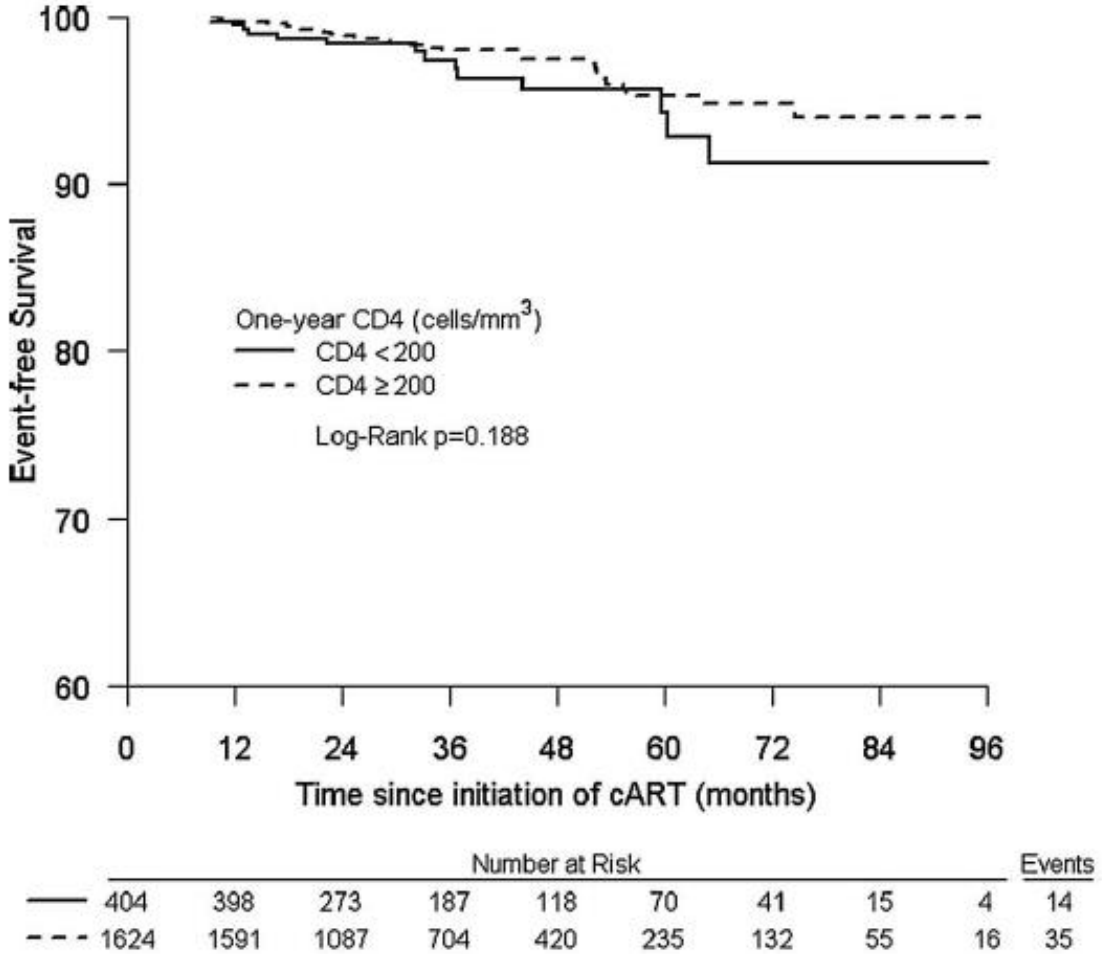
Fig 1. Proportion of patients remaining free from severe non AIDS-related event. List of abbreviations: AIDS, acquired immunodeficiency syndrome; HAART, Highly-active antiretroviral therapy.

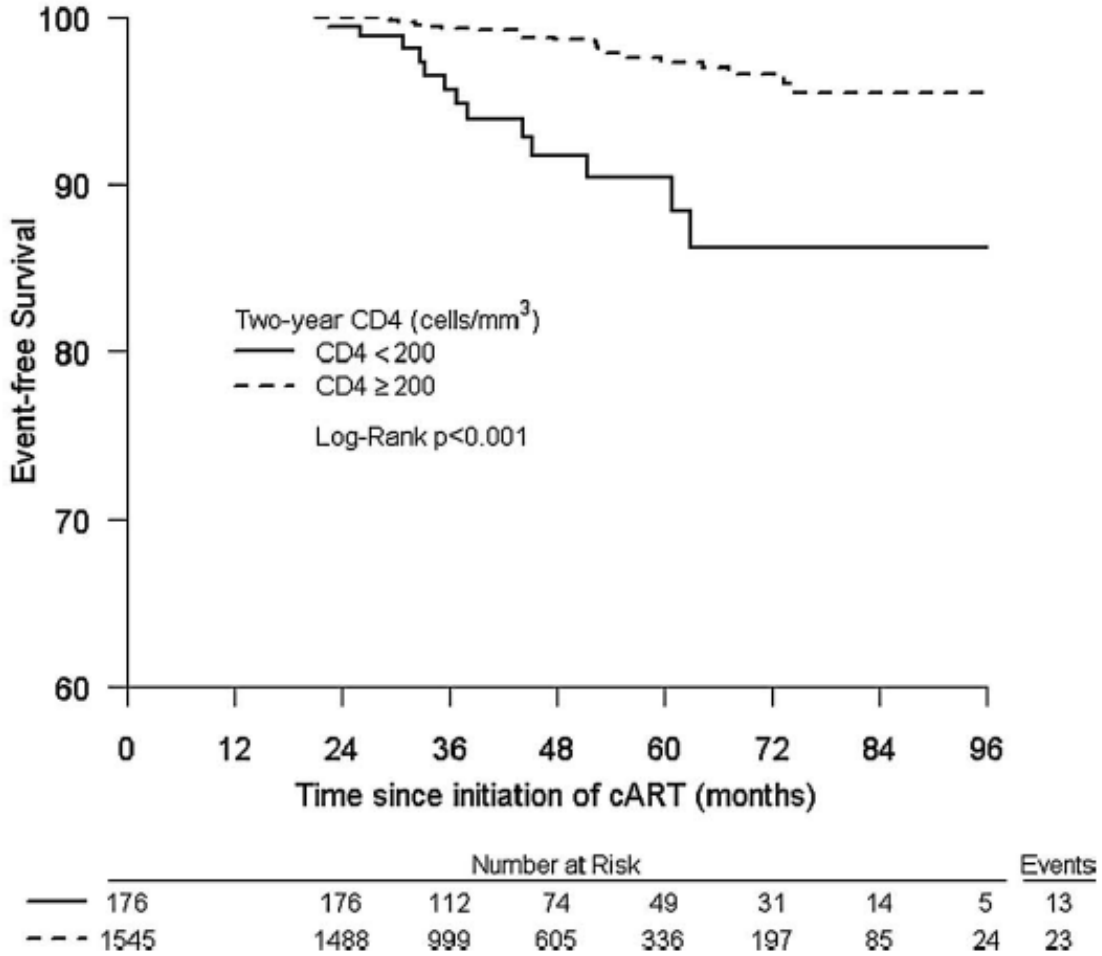
Lapadula et al, Plos One 2015

A CD4$^+$ Cell Count <200 Cells per Cubic Millimeter at 2 Years After Initiation of Combination Antiretroviral Therapy Is Associated With Increased Mortality in HIV-Infected Individuals With Viral Suppression

Mona R. Loutfy, MD, MPH,† Miguel Genebat, MD,‡ David Moore, MDCM, MHSc,§ Janet Raboud, PhD,*‖ Keith Chan, MSc,§ Tony Antoniou, PharmD,*¶ David Milan, BSc,§ Anya Shen, BSc,§ Marina B. Klein, MD,#** Curtis Cooper, MD,†† Nima Machouf, PhD,‡‡ Sean B. Rourke, PhD,*§§‖‖ Anita Rachlis, MD, MEd,*¶¶ Chris Tsoukas, MD,** Julio S. G. Montaner, MD,§## Sharon L. Walmsley, MD, MSc,*‖ Marek Smieja, MD, PhD,**** Ahmed Bayoumi, MD, MSc,*¶‖‖ Edward Mills, PhD,§†† and Robert S. Hogg, PhD,§†††† and the CANOC Collaboration**

(*J Acquir Immune Defic Syndr* 2010;55:451–459)





Loutfy et al, JAIDS 2010

TABLE 3. Correlates of Immunologic Discordance ($CD4^+$ Count <200 Cells/mm^3 at 1 Year and 2 Years) After cART Analyses by Logistic Regression

Variable	One Year After cART (n = 2028)				Two Years After cART (n = 1721)			
	Unadjusted Odds Ratio (95% CI)	*P*	Adjusted Odds Ratio (95% CI)	*P*	Unadjusted Odds Ratio (95% CI)	*P*	Adjusted Odds Ratio (95% CI)	*P*
Age (per decade)	1.17 (1.05 to 1.30)	0.005	1.19 (1.03 to 1.37)	0.015	1.30 (1.11 to 1.51)	0.001	1.23 (1.03 to 1.48)	0.023
Gender (male vs. female)	1.03 (0.77 to 1.38)	0.845	—	—	1.65 (1.01 to 2.70)	0.048	1.86 (1.09 to 3.16)	0.022
Province								
British Columbia	1.00	0.660	—	—	1.00	0.034	—	—
Ontario	0.96 (0.75 to 1.23)		—	—	0.62 (0.42 to 0.89)		—	—
Quebec	0.87 (0.65 to 1.17)		—	—	0.83 (0.56 to 1.25)		—	—
History of injection drug use	2.21 (1.66 to 2.94)	<0.001	2.18 (1.53 to 3.12)	<0.001	3.06 (2.11 to 4.45)	<0.001	2.75 (1.81 to 4.17)	<0.001
Hepatitis C								
Negative	1.00	<0.001	—	—	1.00	<0.001	—	—
Positive	1.63 (1.23 to 2.17)				2.94 (2.01 to 4.30)		—	—
Unknown	0.84 (0.62 to 1.14)				1.75 (1.17 to 2.62)		—	—
Baseline $CD4^+$ count (per 100 cells/mm^3)	0.18 (0.15 to 0.22)	<0.001	0.15 (0.12 to 0.18)	<0.001	0.28 (0.22 to 0.35)	<0.001	0.24 (0.19 to 0.31)	<0.001
Baseline viral load (per $\log_{10}$ copies/mL)	1.17 (0.95 to 1.44)	0.149	0.42 (0.32 to 0.54)	<0.001	0.98 (0.73 to 1.32)	0.910	0.46 (0.33 to 0.65)	<0.001
Baseline ADI (before viral suppression)	3.45 (2.68 to 4.45)	<0.001	—	—	3.25 (2.32 to 4.54)	<0.001	—	—
Third drug class								
NNRTI	1.00	0.010	—	—	1.00	0.735	—	—
Single PI	0.96 (0.62 to 1.48)		—	—	1.07 (0.61 to 1.88)		—	—
Boosted PI	1.39 (1.11 to 1.75)		—	—	0.89 (0.64 to 1.24)		—	—

cART, combination antiretroviral therapy; CI, confidence intervals; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; ADI, AIDS-defining illness.

Long-term Mortality in HIV-Positive Individuals Virally Suppressed for >3 Years With Incomplete CD4 Recovery

Frederik N. Engsig,[1,2] Robert Zangerle,[3] Olga Katsarou,[4] Francois Dabis,[5] Peter Reiss,[6,7] John Gill,[8] Kholoud Porter,[9] Caroline Sabin,[10] Andrew Riordan,[11] Gerd Fätkenheuer,[12] Félix Gutiérrez,[13] Francois Raffi,[14] Ole Kirk,[1,15] Murielle Mary-Krause,[16] Christoph Stephan,[17] Patricia Garcia de Olalla,[18] Jodie Guest,[19] Hasina Samji,[20] Antonella Castagna,[21] Antonella d'Arminio Monforte,[22] Adriane Skaletz-Rorowski,[23] Jose Ramos,[24] Giuseppe Lapadula,[25] Cristina Mussini,[26] Lluís Force,[27] Laurence Meyer,[28] Fiona Lampe,[29] Faroudy Boufassa,[30] Heiner C. Bucher,[31] Stéphane De Wit,[32] Greer A. Burkholder,[33] Ramon Teira,[34] Amy C. Justice,[35,36] Tim R. Sterling,[37] Heidi M. Crane,[38] Jan Gerstoft,[1] Jesper Grarup,[15] Margaret May,[39] Geneviève Chêne,[5] Suzanne M. Ingle,[39] Jonathan Sterne,[39] and Niels Obel[1]; for the Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

Engsig et al (COHERE), Clin Infect Dis 2014

Table 2. Factors Associated With Failure to Achieve CD4 Count >200 Cells/μL After 3 Years of Viral Suppression on Combination Antiretroviral Therapy

Factor	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Age at start of the suppressed period, y		
<30	1 (reference)	1 (reference)
30–39	1.36 (.97–1.89)	1.31 (.93–1.85)
40–49	2.17 (1.56–3.03)	2.04 (1.45–2.88)
≥50	3.98 (2.85–5.55)	4.01 (2.84–5.68)
Route of transmission		
MSM	1 (reference)	1 (reference)
Male heterosexual sex	1.62 (1.32–1.98)	1.50 (1.21–1.85)
Female heterosexual sex	0.81 (.63–1.04)	0.89 (.68–1.15)
Injection drug use	1.96 (1.54–2.48)	2.03 (1.57–2.61)
Other/unknown	2.02 (1.62–2.52)	1.72 (1.37–2.17)
CD4 count at start of suppressed period, cells/μL		
≤25	3.90 (2.86–5.32)	5.21 (3.75–7.23)
26–50	3.39 (2.58–4.44)	4.46 (3.35–5.95)
51–100	3.21 (2.59–3.97)	3.73 (2.99–4.68)
101–150	1.95 (1.57–2.42)	2.08 (1.67–2.60)
151–200	1 (reference)	1 (reference)
Last viral load measurement before start of cART[b], copies/mL		
<100 000	1.07 (.92–1.24)	1.13 (.97–1.33)
≥100 000	1 (reference)	1 (reference)
Year of start of cART		
1996–1997	1 (reference)	1 (reference)
1998–2000	1.28 (.97–1.69)	1.44 (1.07–1.93)
2001 onward	1.07 (.81–1.40)	1.37 (1.02–1.84)
Time from cART initiation to start of suppressed period, mo		
<12	1 (reference)	1 (reference)
≥12	1.73 (1.45–2.06)	2.05 (1.68–2.50)
1 or more AIDS events before start of suppressed period		
No AIDS event	1.17 (1.01–1.35)	0.89 (.76–1.04)
AIDS event	1 (reference)	1 (reference)

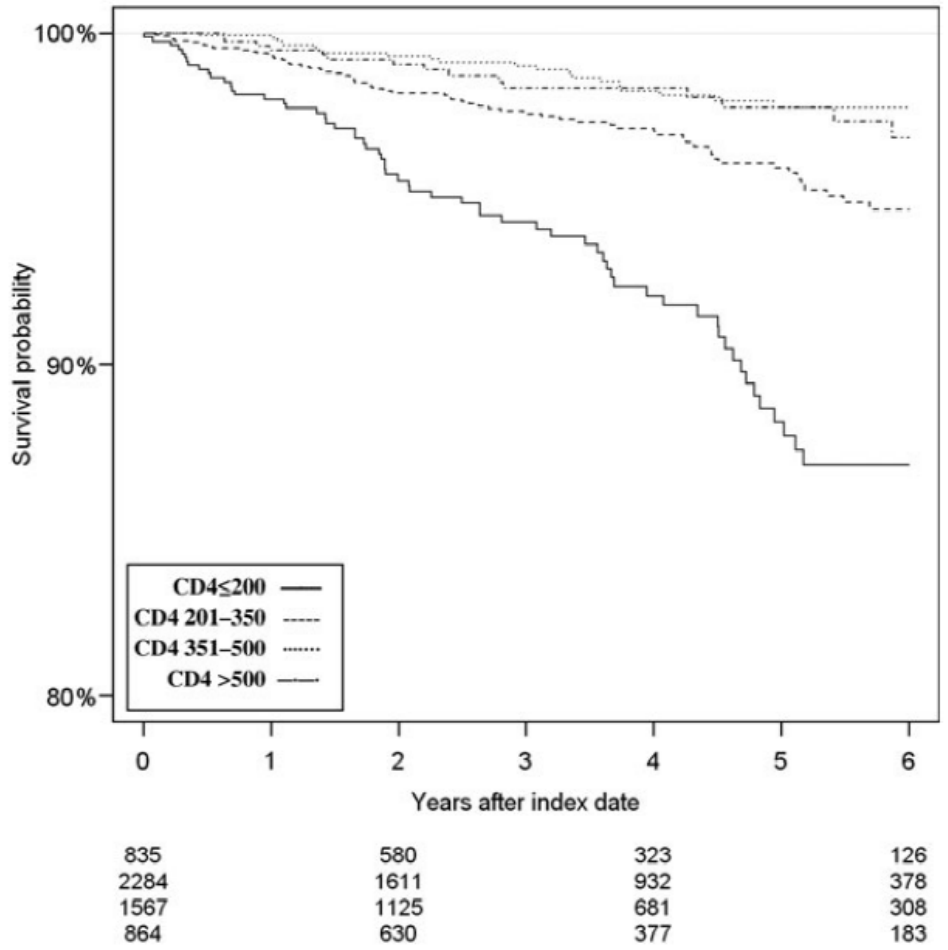


Figure 2. Cumulative probability of survival stratified by CD4 count at the end of the virally suppressed period: ≤200 cells/μL (full line); 201–350 cells/μL (broken line); 351–500 cells/μL (dotted line); and >500 cells/μL (broken and dotted line).

Engsig et al (COHERE), Clin Infect Dis 2014

Conseguenze cliniche di INR

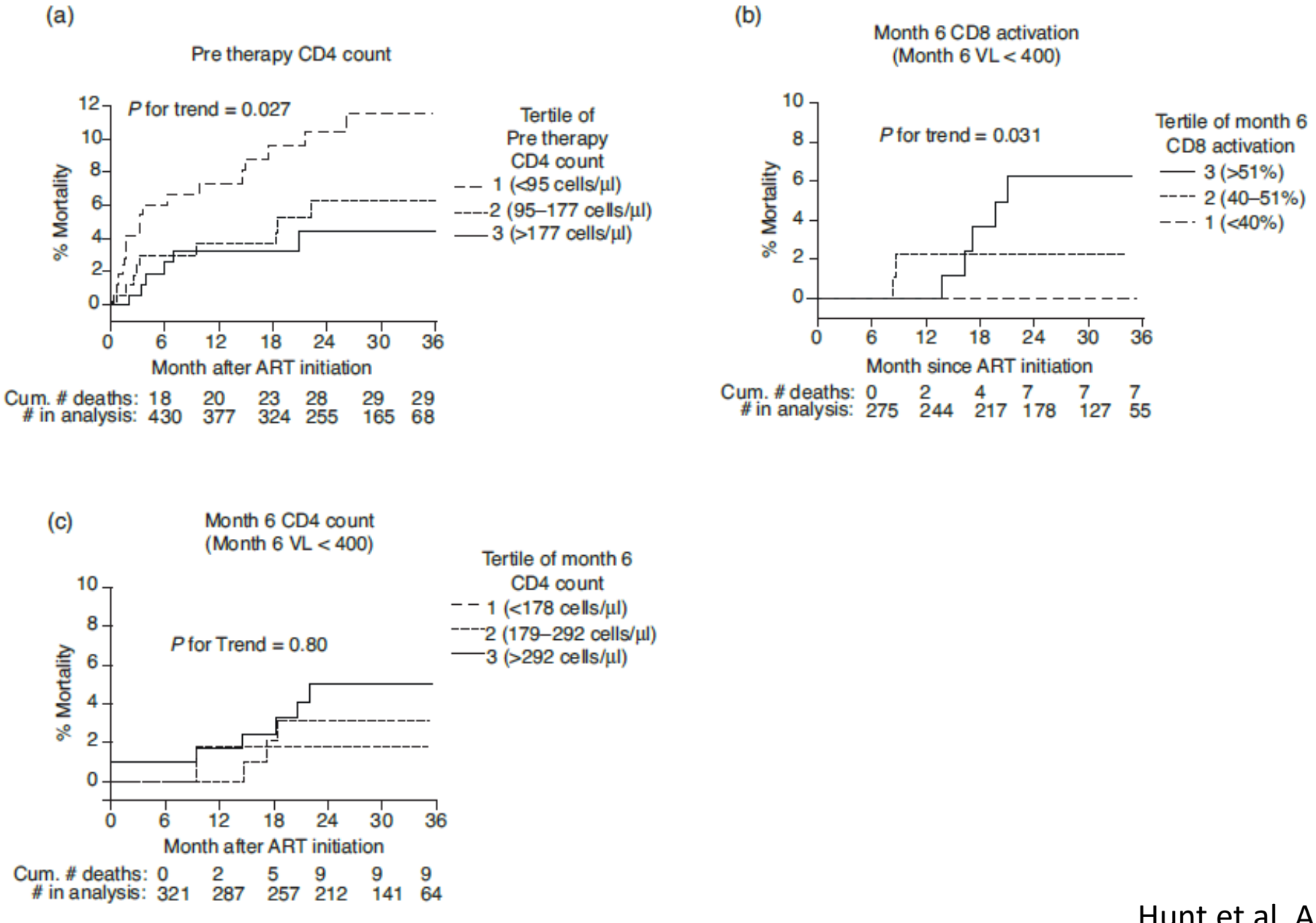
- Prolungare profilassi per PcP? ☒ No
- Avere più mortalità per eventi AIDS? ☑ Sì
- Avere più mortalità per eventi non AIDS? ☑ Sì
- Avere più mortalità in generale? ☑ Sì

Da cosa dipende l’outcome degli INR?

Impact of $CD8^+$ T-cell activation on $CD4^+$ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy

Peter W. Hunt[a], Huyen L. Cao[a,b,c], Conrad Muzoora[d], Isaac Ssewanyana[b], John Bennett[a], Nneka Emenyonu[d,e], Annet Kembabazi[d], Torsten B. Neilands[a], David R. Bangsberg[d,e], Steven G. Deeks[a] and Jeffrey N. Martin[a]

AIDS 2011, **25**:2123–2131



Hunt et al, AIDS 2011

OPEN ACCESS Freely available online

PLOS MEDICINE

Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

Lewis H. Kuller[1], Russell Tracy[2], Waldo Belloso[3], Stephane De Wit[4], Fraser Drummond[5], H. Clifford Lane[6], Bruno Ledergerber[7], Jens Lundgren[8], Jacqueline Neuhaus[9], Daniel Nixon[10], Nicholas I. Paton[11], James D. Neaton[9*], for the INSIGHT SMART Study Group

Kuller et al, Plos Med 2008

Table 5. Risk of Death Associated with Latest Level of Each Biomarker

Biomarker	OR[a]	95% CI	*p*-Value
hsCRP (µg/ml)	2.4	1.4–4.2	0.003
Amyloid A (mg/l)	1.4	1.0–1.9	0.09
Amyloid P (µg/ml)	0.7	0.4–1.0	0.04
IL-6 (pg/ml)	2.0	1.2–3.1	0.006
D-dimer (µg/ml)	2.2	1.1–4.1	0.02
F1.2 (pmol/l)	1.1	0.7–1.7	0.77

Kuller et al, Plos Med 2008

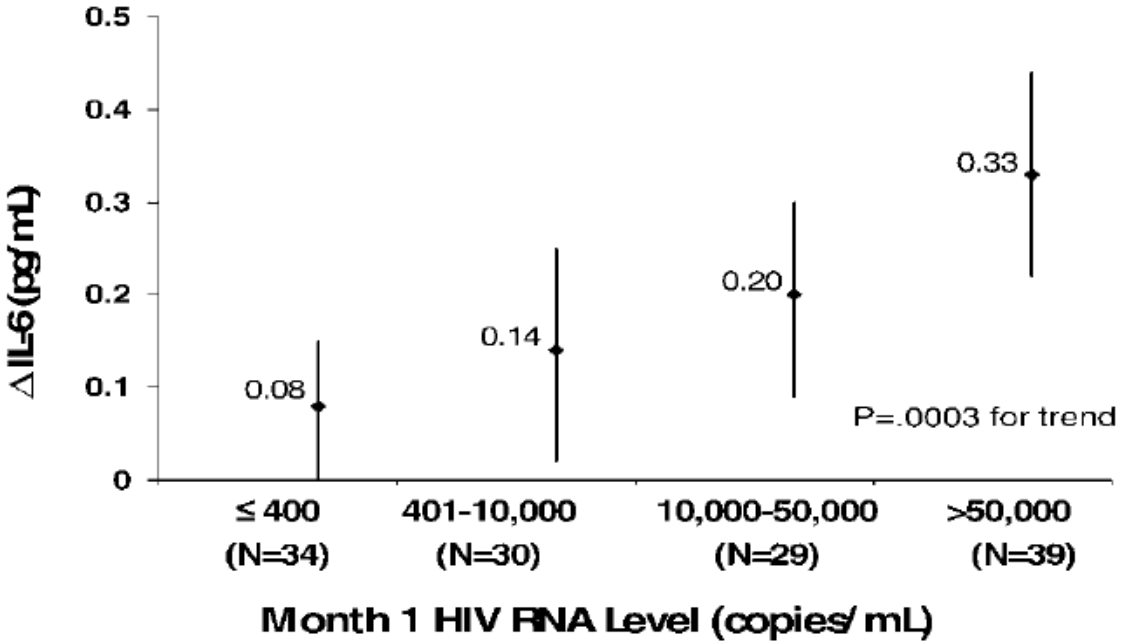


Figure 3. Change in Log_{10} IL-6 (pg/ml) from Baseline to 1 mo According to HIV-RNA Level at 1 mo for Participants in the Drug Conservation (DC) Group (CD4+ Guided Intermittent ART) with an HIV-RNA level 400 Copies/ml or Less at Baseline

doi:10.1371/journal.pmed.0050203.g003

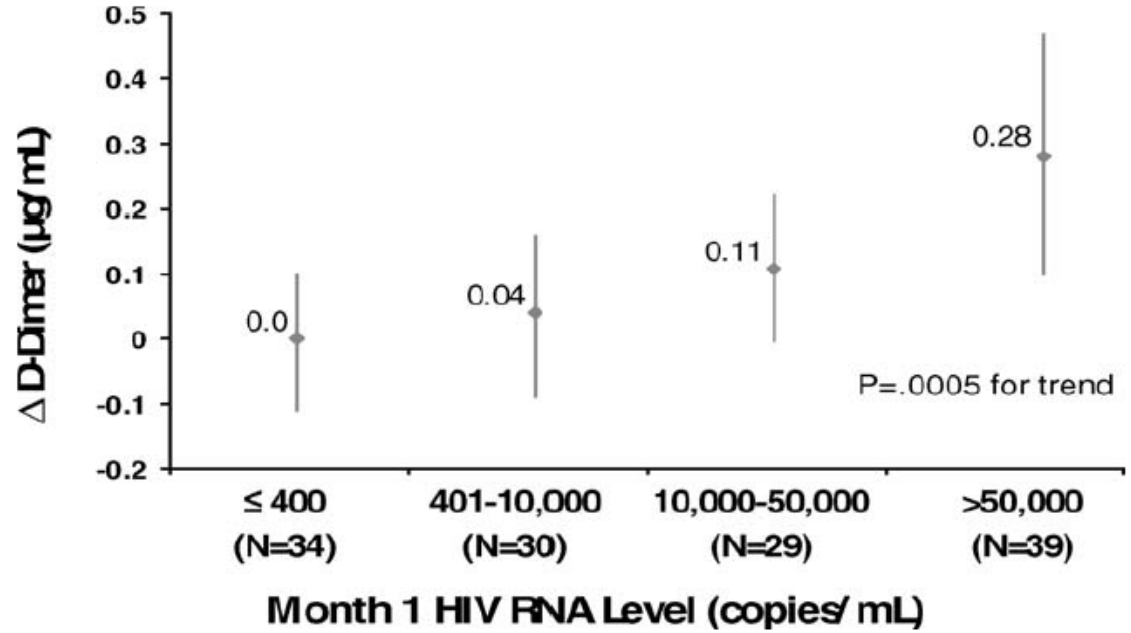


Figure 4. Change in Log_{10} D-dimer (μg/ml) from Baseline to 1 mo According to HIV-RNA Level at 1 mo for Participants in the Drug Conservation (DC) Group (CD4+ Guided Intermittent ART) with an HIV-RNA level 400 Copies/ml or less at Baseline

doi:10.1371/journal.pmed.0050203.g004

Kuller et al, Plos Med 2008

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PLoS one

KIR-HLA Genotypes in HIV-Infected Patients Lacking Immunological Recovery despite Effective Antiretroviral Therapy

Alessandro Soria[1]*, Franca Rosa Guerini[2], Alessandra Bandera[1], Elisabetta Bolognesi[2], Alessia Uglietti[3], Caterina Fusco[4], Patrizia Zucchi[5], Renato Maserati[3], Giuliano Rizzardini[5], Mario Clerici[2,6], Andrea Gori[1]

Results: The frequency of *KIR2DL3* allele was significantly higher in FR than in INR (83.7% vs. 62%, $P=0.005$). The functional compound genotype *HLA-C1*$^+$*/KIR2DL3*$^+$, even at multivariable analysis, when adjusted for nadir CD4$^+$ T-cell count, was associated with reduced risk of INR status: odds ratio (95% Confidence Intervals) 0.34 (0.13−0.88), $P=0.03$.

Conclusions: Reduced presence of the inhibitory *KIR2DL3* genotype detected in INR might provoke an imbalance in NK function, possibly leading to increased immune activation, impaired killing of latently infected cells, and higher proviral burden. These factors would hinder full immune recovery during therapy.

Soria et al, Plos One 2011

Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection

Peter W. Hunt,[1] Elizabeth Sinclair,[1] Benigno Rodriguez,[2] Carey Shive,[2] Brian Clagett,[2] Nicholas Funderburg,[3] Janet Robinson,[2] Yong Huang,[4] Lorrie Epling,[1] Jeffrey N. Martin,[1,5] Steven G. Deeks,[1] Curtis L. Meinert,[6] Mark L. Van Natta,[6] Douglas A. Jabs,[6,7] and Michael M. Lederman[2]

Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non–AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment

Allan R. Tenorio,[1] Yu Zheng,[3] Ronald J. Bosch,[3] Supriya Krishnan,[3] Benigno Rodriguez,[4] Peter W. Hunt,[5] Jill Plants,[2] Arjun Seth,[4] Cara C. Wilson,[6] Steven G. Deeks,[5] Michael M. Lederman,[4] and Alan L. Landay[2]

Results. Higher IL-6 level, sTNFR-I level, sTNFR-II level, KT ratio, and D-dimer level at year 1 were associated with the occurrence of a non–AIDS-defining event. Significant associations were also seen between non–AIDS-defining events and values of these biomarkers in specimens obtained at baseline and the pre-event time points. Effects remained significant after control for confounders. T-cell activation was not significantly related to outcomes.

Conclusions. Interventional trials to decrease the incidence of non–AIDS-defining events among HIV-infected persons with virological suppression should consider targeting the pathways represented by these soluble markers.

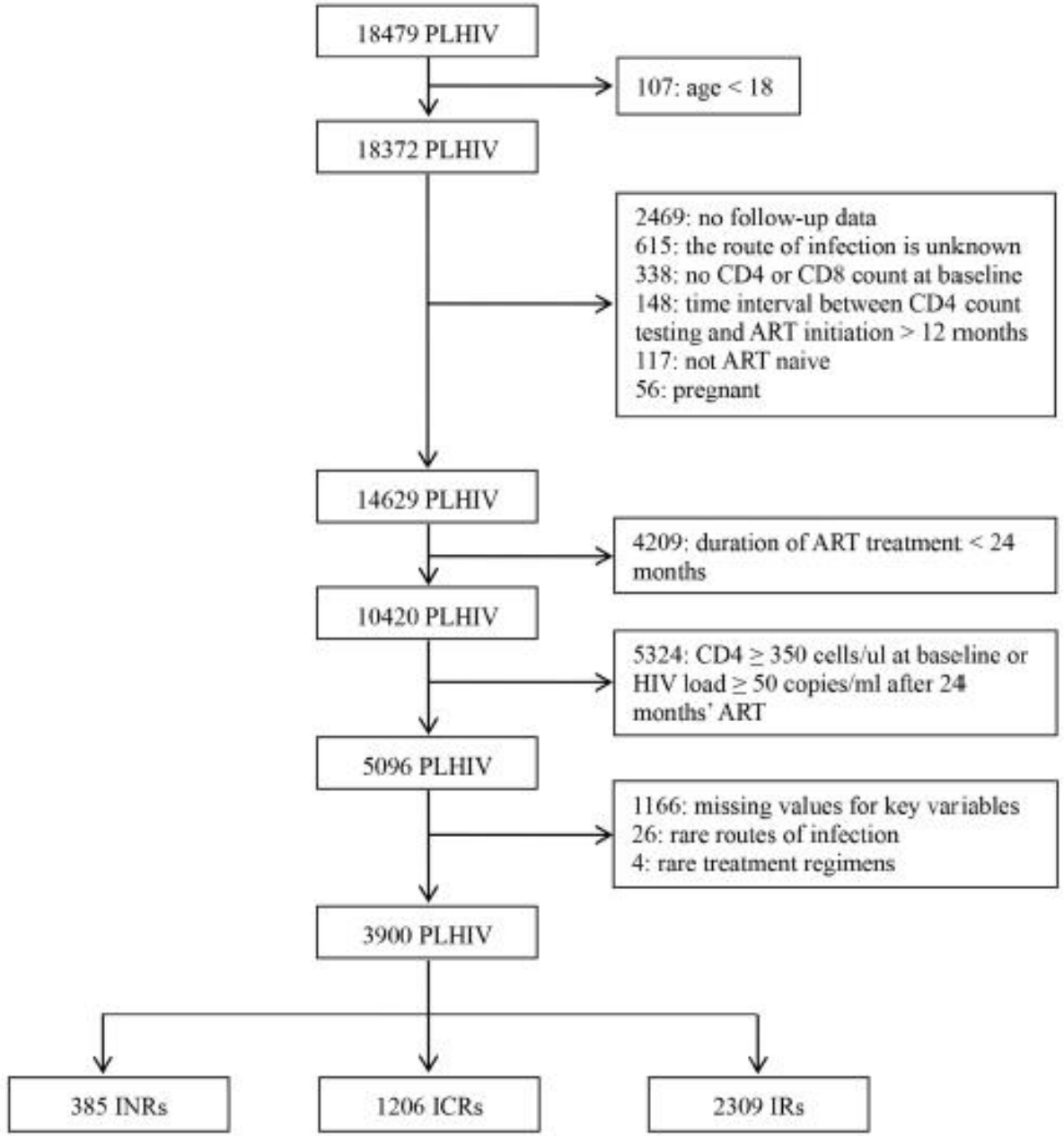
Zhao *et al. BMC Infectious Diseases* (2024) 24:138
https://doi.org/10.1186/s12879-024-09021-9

BMC Infectious Diseases

RESEARCH Open Access

Factors associated with immunological non-response after ART initiation: a retrospective observational cohort study

Heping Zhao[1,2†], Anping Feng[2†], Dan Luo[2†], Tanwei Yuan[2], Yi-Fan Lin[2], Xuemei Ling[1], Huolin Zhong[1], Junbin Li[1], Linghua Li[1*] and Huachun Zou[3,4,5*]



Zhao et al, BMC Infect Dis 2024

Table 2 Factors associated with immunological incomplete response and immunological non-response among PLHIV

Variable	ICRs			INRs		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Sex						
Female	1.00			1.00		
Male	1.50	1.17–1.92	**0.001**	2.07	1.39–3.09	**< 0.001**
Age (years)						
18–29	1.00			1.00		
30–39	0.91	0.74–1.13	0.406	1.06	0.71–1.58	0.789
40–49	1.16	0.88–1.52	0.290	2.05	1.29–3.25	**0.002**
50–59	1.29	0.90–1.85	0.162	4.04	2.33-7.00	**< 0.001**
≥ 60	1.41	0.88–2.26	0.152	5.51	2.84–10.67	**< 0.001**
HBV						
Positive	1.24	0.98–1.58	0.079	1.63	1.14–2.34	**0.008**
Negative	1.00			1.00		
HCV						
Positive	1.27	0.79–2.06	0.328	2.01	1.01–4.02	**0.047**
Negative	1.00			1.00		
Baseline CD4 + cell count (cells/μl)						
200–350	1.00			1.00		
50–200	5.14	4.05–6.52	**< 0.001**	40.20	16.83–96.01	**< 0.001**
< 50	10.38	7.32–14.70	**< 0.001**	215.67	85.62-543.26	**< 0.001**
Baseline CD4+/CD8 ratio						
≥ 0.2	1.00			1.00		
< 0.2	1.57	1.29–1.89	**< 0.001**	2.93	1.98–4.34	**< 0.001**
ART regimens						
NRTIs + NNRTIs	1.00			1.00		
NRTIs + PIs	0.70	0.49–0.98	**0.037**	0.47	0.26–0.82	**0.008**
NRTIs + INSTIs	0.71	0.40–1.29	0.265	0.84	0.41–1.73	0.632
NRTIs	0.62	0.35–1.09	0.098	1.13	0.61–2.10	0.698

Zhao et al, BMC Infect Dis 2024

The impact of age on the prognostic capacity of CD8$^+$ T-cell activation during suppressive antiretroviral therapy

Judith J. Lok[a,b], Peter W. Hunt[c], Ann C. Collier[d], Constance A. Benson[e], Mallory D. Witt[f], Amneris E. Luque[g], Steven G. Deeks[h] and Ronald J. Bosch[b]

Table 5. Estimated odds ratios, 95% confidence interval, and *P*-values for the probability of events in years 2–5 after initiation of antiretroviral treatment: participants 50 years and older, had everyone continued to have viral suppression on antiretroviral treatment.

	Univariate OR	Adjusted OR CD8$^+$ T-cell activation[a]	Multivariable model
CD8$^+$ T-cell activation year 1 [per 10 units (%) higher][b]	1.42 (1.07, 2.47) ($P=0.015$)	–	1.51 (1.10, 2.91) ($P=0.008$)
CD4 sqrt[c] year 1 (per 3 units higher)[d]	1.13 (0.84, 1.54) ($P=0.43$)	1.50 (1.10, 2.62)	1.22 (0.89, 1.77) ($P=0.21$)
Age (per 10 years older)	1.14 (0.31, 3.55) ($P=0.81$)	1.43 (1.06, 2.64)	0.89 (0.15, 3.54) ($P=0.90$)

CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study

*Cristina Mussini, Patrizia Lorenzini, Alessandro Cozzi-Lepri, Giuseppe Lapadula, Giulia Marchetti, Emanuele Nicastri, Antonella Cingolani, Miriam Lichtner, Andrea Antinori, Andrea Gori, Antonella d'Arminio Monforte, for the Icona Foundation Study Group**

Findings We included 3236 participants, enrolled between Jan 22, 1997, and Feb 25, 2013. At the start of ART, median CD4/CD8 ratio in our population was 0·39 (IQR 0·26–0·55). 458 (14%) patients reached a CD4/CD8 ratio of 1 or more; the estimated probability of normalisation was 4·4% (95% CI 3·7–5·2) by 1 year from baseline, 11·5% (10·2–13·0) by 2 years, and 29·4% (26·7–32·4) by 5 years. Factors associated with normalisation were high pre-ART CD4 cell counts, a high CD4/CD8 ratio at baseline, and negative cytomegalovirus serological findings. The incidence rate of non-AIDS-defining events for patients with a CD4/CD8 ratio of less than 0·30 (4·2 per 100 patient-years, 95% CI 3·4–5·3) was double that for those with a ratio of 0·30–0·45 (2·3, 2·1–2·5) or more than 0·45 (2·2, 1·7–2·9). A ratio of less than 0·30 was independently associated with an increased risk of non-AIDS-defining events or death compared with one of more than 0·45.

Mussini et al, Lancet HIV 2015

Fattori correlati a INR

BIOLOGICI

- Aumento immunoattivazione
- Fattori genetici correlati all'immunità innata NK
- Aumento permeabilità intestinale
- Aumento fattori solubili dell'infiammazione/coagulazione

CLINICI

- Età
- (sesso maschile)
- HCV
- CD4 basali, CD4/CD8 ratio

Opzioni terapeutiche

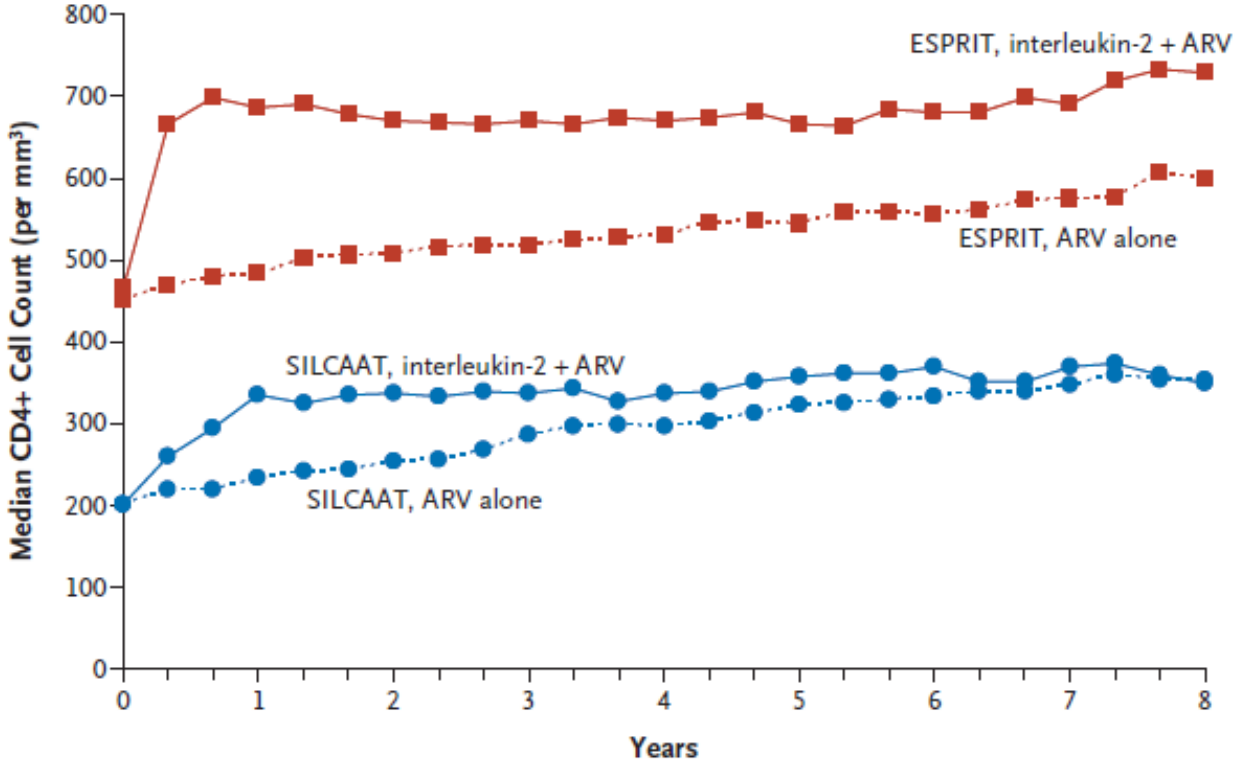
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-2 Therapy in Patients with HIV Infection

The INSIGHT–ESPRIT Study Group and SILCAAT Scientific Committee*

Abrams et al, NEJM 2009

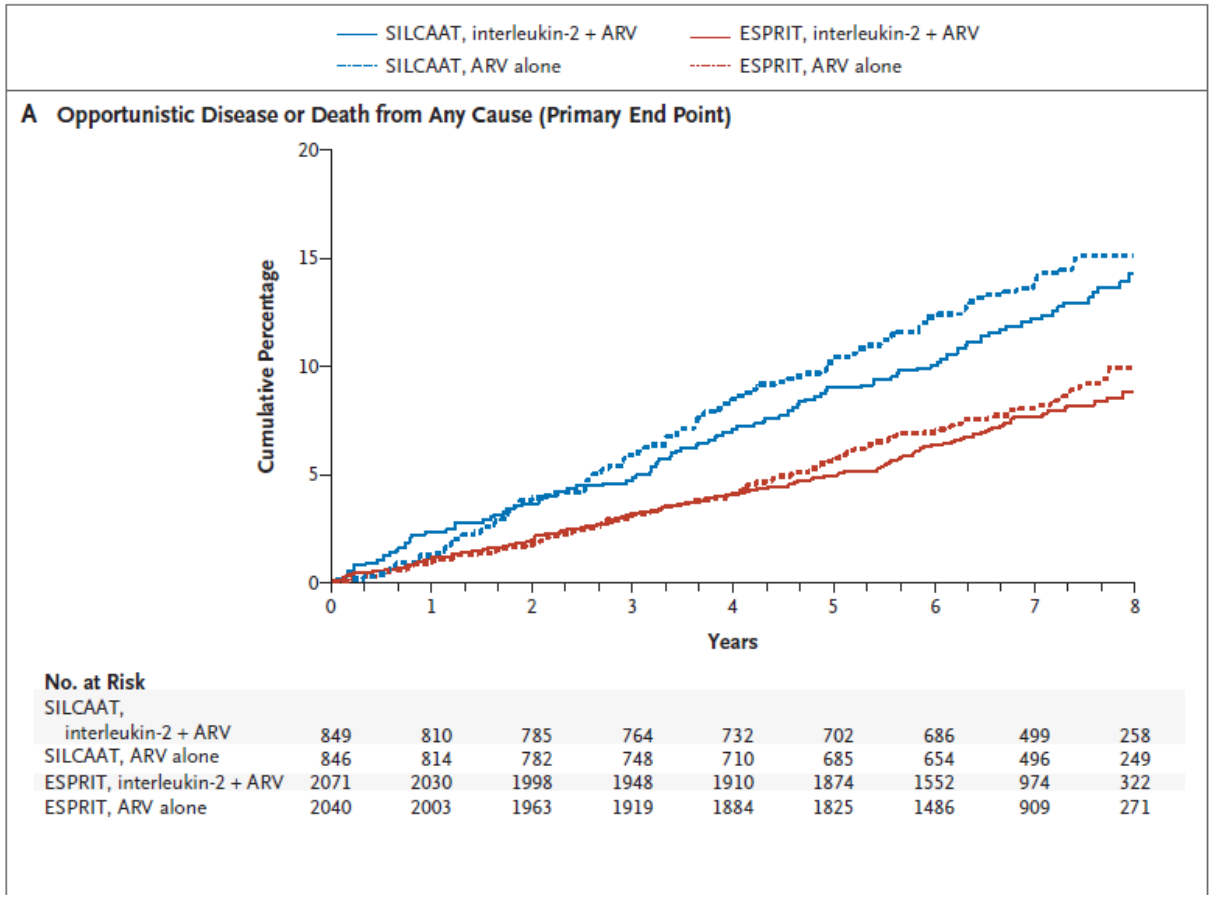


No. of Patients									
SILCAAT, interleukin-2 + ARV	849	722	650	635	648	623	597	447	254
SILCAAT, ARV alone	845	754	679	666	632	632	603	453	233
% Receiving interleukin-2 during yr	97.8	39.8	23.6	18.4	14.8	12.0	7.5	4.2	
ESPRIT, interleukin-2 + ARV	2071	1890	1842	1809	1768	1732	1415	887	297
ESPRIT, ARV alone	2040	1928	1862	1803	1740	1649	1349	831	255
% Receiving interleukin-2 during yr	96.2	37.9	28.7	22.3	17.7	13.7	12.5	9.6	

Figure 1. Median CD4+ Cell Counts during the Study Period, According to Study and Treatment Group.

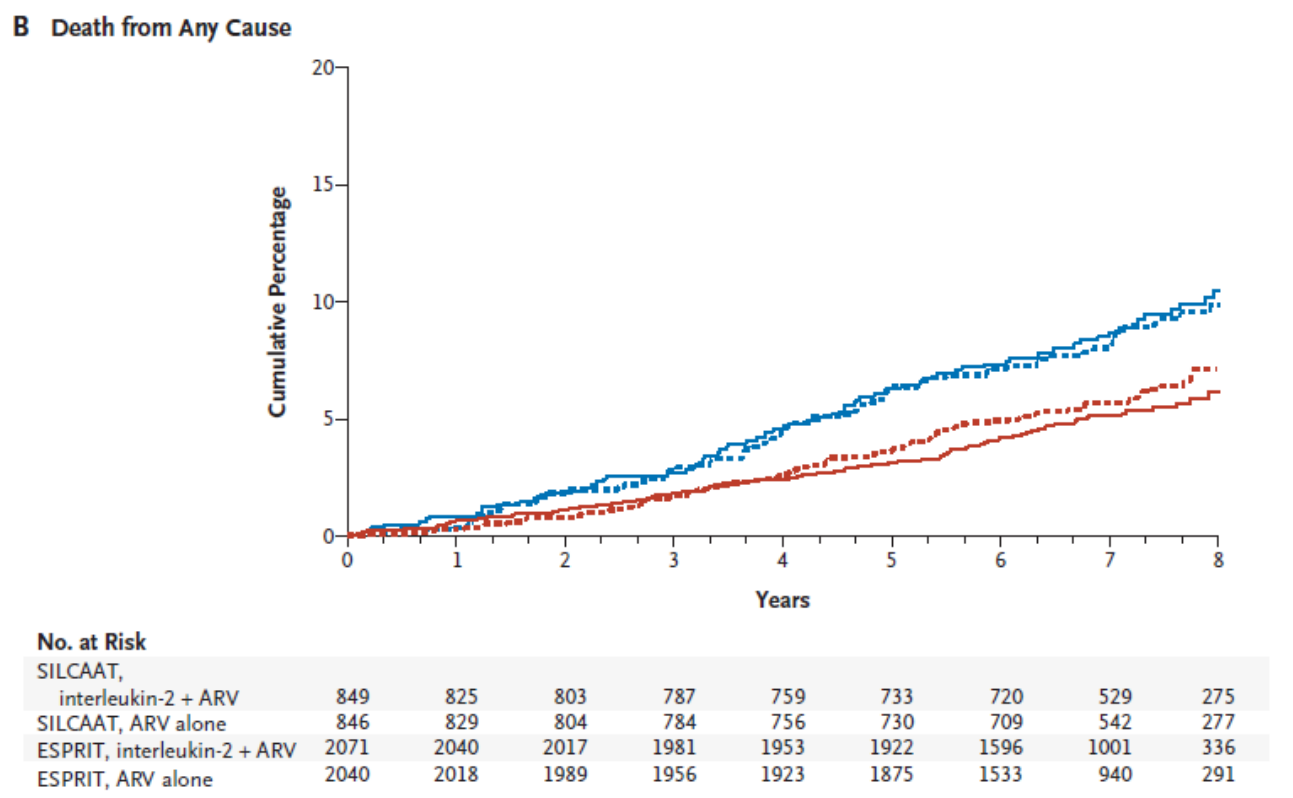
The median CD4+ cell counts are shown for the groups receiving interleukin-2 plus antiretroviral therapy (ARV) and the groups receiving ARV alone in the SILCAAT study and ESPRIT. The counts during the first 30 days after a cycle of interleukin-2 are not stable and therefore were excluded. Also shown are the percentages of patients assigned to receive interleukin-2 who were taking the drug during each year of the study.

Abrams et al, NEJM 2009



No. at Risk

SILCAAT, interleukin-2 + ARV	849	810	785	764	732	702	686	499	258
SILCAAT, ARV alone	846	814	782	748	710	685	654	496	249
ESPRIT, interleukin-2 + ARV	2071	2030	1998	1948	1910	1874	1552	974	322
ESPRIT, ARV alone	2040	2003	1963	1919	1884	1825	1486	909	271



No. at Risk

SILCAAT, interleukin-2 + ARV	849	825	803	787	759	733	720	529	275
SILCAAT, ARV alone	846	829	804	784	756	730	709	542	277
ESPRIT, interleukin-2 + ARV	2071	2040	2017	1981	1953	1922	1596	1001	336
ESPRIT, ARV alone	2040	2018	1989	1956	1923	1875	1533	940	291

Abrams et al, NEJM 2009

Table 2. Hazard Ratios for the Primary End Point and Major Secondary End Points in SILCAAT and ESPRIT, According to Treatment Group.

End Point*	Interleukin-2 + Antiretroviral Therapy	Antiretroviral Therapy Alone	Hazard Ratio for Interleukin-2 (95% CI)	P Value
	no. of patients (rate/100 person-yr)			
SILCAAT				
Primary end point: opportunistic disease or death from any cause	110 (1.94)	119 (2.13)	0.91 (0.70–1.18)	0.47
Death from any cause	81 (1.38)	77 (1.31)	1.06 (0.77–1.44)	0.73
Opportunistic disease	49 (0.86)	66 (1.18)	0.73 (0.51–1.06)	0.10
Grade 4 event	203 (3.93)	186 (3.58)	1.10 (0.90–1.34)	0.35
ESPRIT				
Primary end point: opportunistic disease or death from any cause	159 (1.14)	165 (1.21)	0.94 (0.75–1.16)	0.55
Death from any cause	107 (0.75)	116 (0.83)	0.90 (0.69–1.17)	0.42
Opportunistic disease	68 (0.49)	63 (0.46)	1.05 (0.75–1.48)	0.78
Grade 4 event	466 (3.80)	383 (3.09)	1.23 (1.07–1.41)	0.003

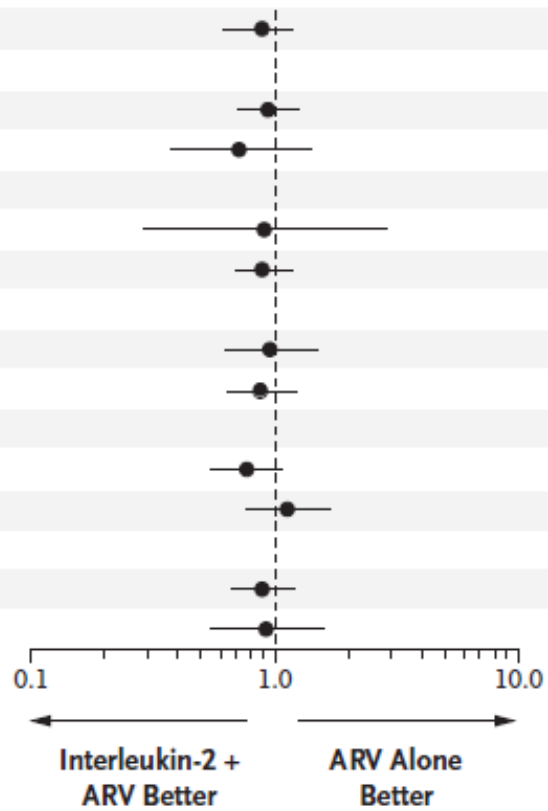


* Grade 4 clinical events were defined as potentially life-threatening events (excluding opportunistic diseases) requiring medical intervention (see toxicity table at http://rcc.tech-res.com).

Abrams et al, NEJM 2009

A SILCAAT

Subgroup	Difference in CD4+ Cell Count (per mm³)	Interleukin-2 + ARV	ARV alone	Hazard Ratio for Interleukin-2 (95% CI)	P Value for Interaction
		no. with an event (rate/100 person-yr)			
All patients	53.0±6.5	110 (1.94)	119 (2.13)	0.91	0.47
Sex					0.47
Male	56.1±6.1	96 (2.01)	98 (2.12)	0.94	
Female	40.3±13.8	14 (1.58)	21 (2.19)	0.72	
Race or ethnic group					0.98
Black	75.4±20.2	5 (1.21)	7 (1.33)	0.91	
White or other	52.4±5.8	105 (2.00)	112 (2.22)	0.90	
Age					0.98
<40 yr	46.9±8.3	41 (1.56)	41 (1.62)	0.96	
≥40 yr	59.2±7.4	69 (2.26)	78 (2.56)	0.88	
Baseline CD4+ cell count (per mm³)					0.12
<200	30.3±7.5	59 (2.19)	75 (2.86)	0.77	
≥200	75.1±8.1	51 (1.71)	44 (1.49)	1.14	
HIV RNA (copies/ml)					0.92
≤500	63.5±6.1	83 (1.79)	92 (2.00)	0.90	
>500	17.6±11.7	27 (2.61)	27 (2.79)	0.93	



Abrams et al, NEJM 2009

In summary, the results of the SILCAAT study and ESPRIT indicate that interleukin-2 offers no clinical benefit as compared with antiretroviral therapy alone. Whether these findings are relevant to other immunotherapies, such as interleukin-7,[27] is uncertain. The precise role of the immune system in the pathogenesis of HIV infection may benefit from a reevaluation as a consequence of our results. Our data indicate that all CD4+ cells may not be equal with respect to host defense and that improvement in the prognostic or surrogate value of CD4+ counts requires refinement in measurement.

Abrams et al, NEJM 2009

Se alzare i CD4 non serve, che bisogna fare?

International Journal of Infectious Diseases 14 (2010) e322–e327

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journal homepage: www.elsevier.com/locate/ijid

Eradication of *Helicobacter pylori* can facilitate immune reconstitution in HIV-1-infected immunological non-responders

Eli Magen [a,b,1,*], Daniel Elbirt [a,1], Nancy Agmon-Levin [a], Joseph Mishal [b], Zev Sthoeger [a]

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Magen et al, Int J Infect Dis 2010

Table 1
Demographic and immunological characteristics at baseline (time of *Helicobacter pylori* diagnosis/eradication)

	Group 1[a]	Group 2[a]	*p*-Value
Number of patients (male/female)	11 (6/5)	15 (7/8)	NS
Age (years)	44.5 ± 15.5	45.2 ± 13.9	NS
Time from HIV diagnosis, years	5.9 ± 2.4	6.2 ± 2.8	NS
Cell counts and percentages[b]			
CD4 cells/mm^3	220.3 ± 111.9	241.4 ± 120.8	NS
CD4%	15.6 ± 8.5	16.8 ± 7.8	NS
CD8 cells/mm^3	698.3 ± 158.7	736.5 ± 187.2	NS
CD8%	68.3 ± 12.7	70.1 ± 16.8	NS
CD4/CD8	0.32 ± 0.11	0.33 ± 0.13	NS
Duration of HAART, mean ± SD (years)	2.3 ± 1.1	2.6 ± 1.4	NS
HAART[c]			
AZT + 3TC + NFV	4 (36.4)	3 (20)	
D4T + 3TC + NFV	1 (9.1)	2 (13.3)	
AZT + 3TC + IDV	0 (0)	1 (6.7)	
AZT + 3TC + IDV/RTV	2 (18.2)	3 (20)	
D4T + 3TC + IDV/RTV	1 (9.1)	2 (13.3)	
AZT + 3TC + EFV	2 (18.2)	3 (20)	
AZT + 3TC + NVP	1 (9.1)	1 (6.7)	

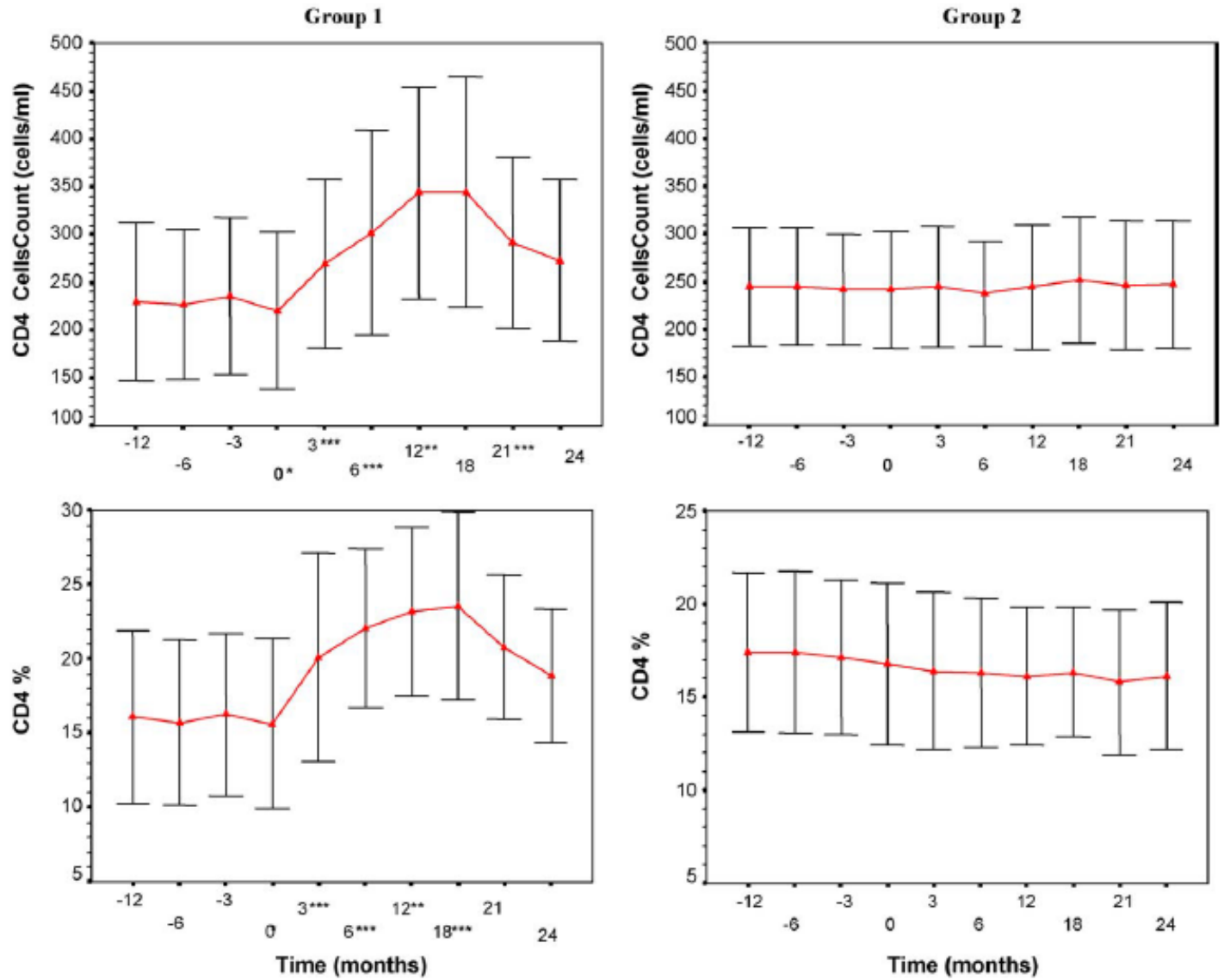
Results are mean ± standard deviation or *n* (%) unless otherwise stated.

[a] Group 1: 11 patients who underwent successful *Helicobacter pylori* eradication with triple therapy; group 2: 15 patients who refused *H. pylori* triple therapy. All patients had *H. pylori* co-infection as determined by a positive urea breath test and were defined as immunologic non-responders.

[b] Cell counts and percentages at baseline.

[c] HAART (highly active antiretroviral treatment): AZT, zidovudine (300 mg bid); 3TC, lamivudine (150 mg bid); D4T, stavudine (40 mg bid); NFV, nelfinavir (750 mg tid); IDV, indinavir (400 mg tid); IND/RTV, indinavir 400 mg/ritonavir 100 mg bid; EFV, efavirenz (600 mg qd); NVP, nevirapine (200 mg bid).

Magen et al, Int J Infect Dis 2010



Magen et al, Int J Infect Dis 2010

The impact of DAA-mediated HCV eradication on $CD4^+$ and $CD8^+$ T lymphocyte trajectories in HIV/HCV coinfected patients: Data from the ICONA Foundation Cohort

Alessandra Bandera[1,2] | Patrizia Lorenzini[3] | Lucia Taramasso[1,4] | Alessandro Cozzi-Lepri[5] | Giuseppe Lapadula[6] | Cristina Mussini[7] | Annalisa Saracino[8] | Francesca Ceccherini-Silberstein[9] | Massimo Puoti[10] | Eugenia Quiros-Roldan[11] | Francesca Montagnani[12] | Andrea Antinori[3] | A. d'Arminio Monforte[13] | Andrea Gori[1,2] | For the Icona Foundation Cohort

Bandera et al., J Viral Hepat 2021

TABLE 3 Unadjusted and adjusted difference in the change of CD4, CD8, ratio and white cells by means of linear regression in the two strata of patients: a) treated with RBV and b) not treated.

Biomarker	Unadjusted difference in change		Adjusted[a] difference in change	
	Variation Pre-Post DAA (95% CI)	p-value	Variation Pre-Post DAA (95% CI)	p-value
a. Patients treated with RBV, N = 332				
CD4				
Post-DAA vs. pre-DAA	36.2 (−5.7, 78.0)	0.090	33.9 (−13.6, 81.5)	0.161
CD8^				
Post-DAA vs. pre-DAA	119.0 (30.3, 207.7)	0.009	141.2 (40.3, 242.1)	0.006
Ratio				
Post-DAA vs. pre-DAA	−0.021 (−0.074, 0.033)	0.095	−0.022 (−0.083, 0.038)	0.470
White blood cells				
Post-DAA vs. pre-DAA	407 (99, 714)	0.010	279 (−162, 720)	0.214
b. Patients NOT treated with RBV, N = 607				
CD4				
Post-DAA vs. pre-DAA	7.2 (−69.5, 84.0)	0.853	−3.9 (−91.0, 83.2)	0.930
CD8^				
Post-DAA vs. pre-DAA	−173.7 (−324.8, −22.6)	0.024	−204.3 (−375.0, −33.4)	0.019
Ratio				
Post-DAA vs. pre-DAA	−0.009 (−0.080, 0.060)	0.783	−0.033 (−0.112, 0.047)	0.418
White blood cells				
Post-DAA vs. pre-DAA	734 (487, 982)	<0.001	710 (359, 1061)	<0.001

[a]Adjusted for time between measurements, age, stiffness and HCV genotype; ^the difference in change of CD8 is not adjusted for age.

Bandera et al., J Viral Hepat 2021

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SHORT COMMUNICATION

CD4+ T-cell recovery in HIV/hepatitis C co-infected patients following successful hepatitis C treatment

Patrick Ryscavage[1] | Siham Hussien[2] | Hyunuk Seung[3] | Lauren Hynicka[3]

HIV Med. 2024;1–6.

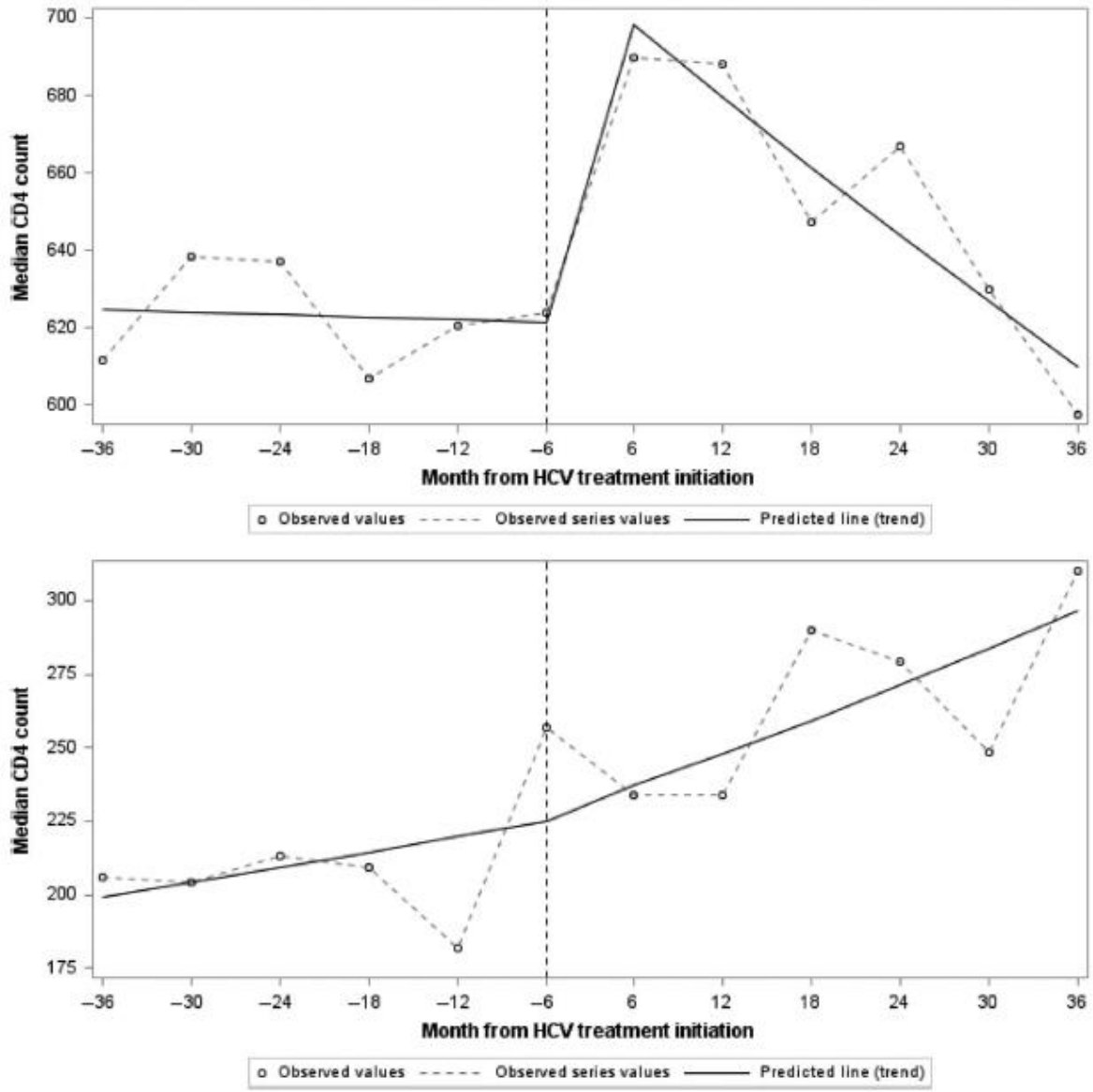
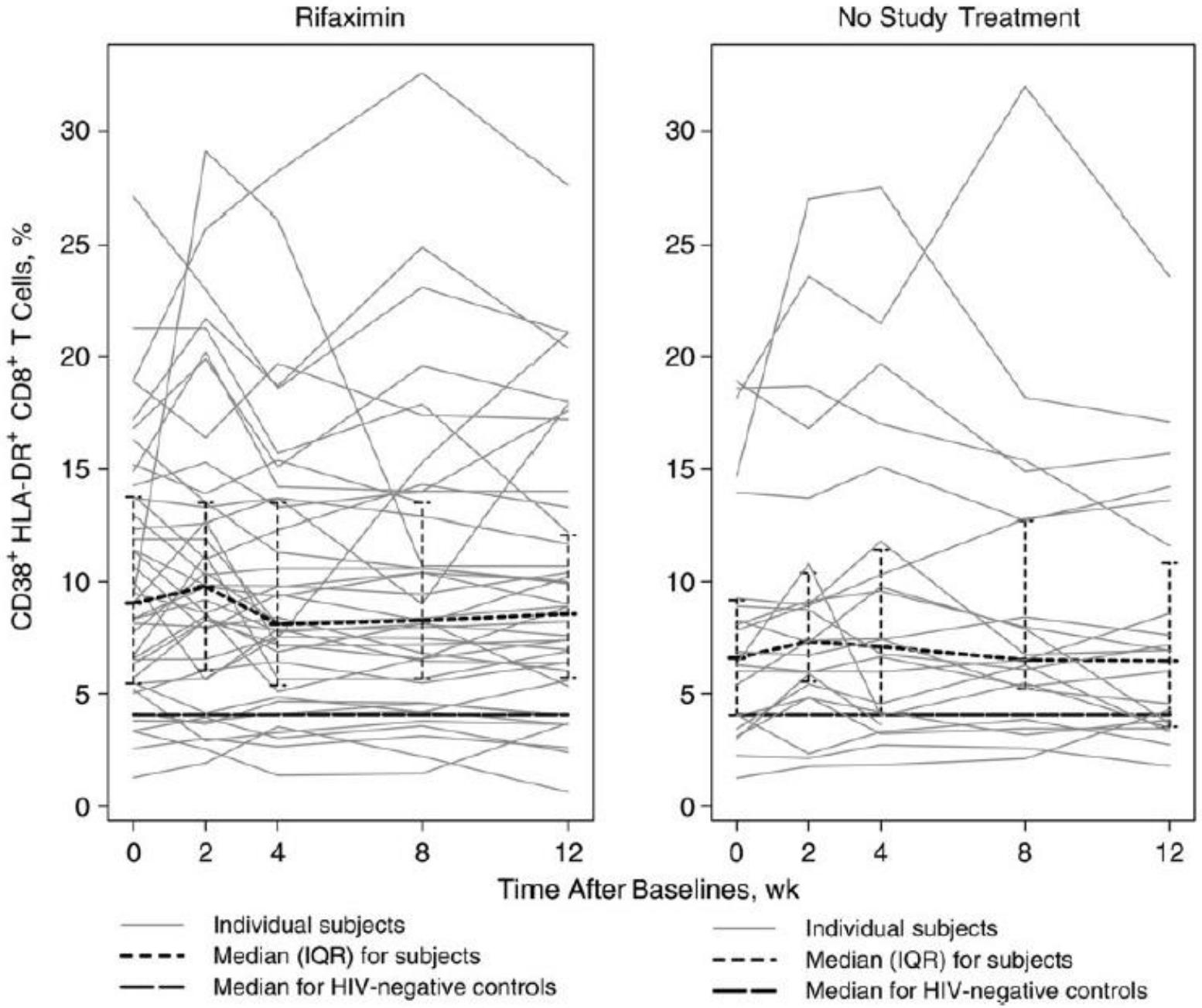


FIGURE 1 Interrupted time series analysis of median CD4+ T-cell counts before and after hepatitis C virus (HCV) treatment for entire cohort (upper image) and immunological non-responders (lower image).

Rifaximin has a Marginal Impact on Microbial Translocation, T-cell Activation and Inflammation in HIV-Positive Immune Non-responders to Antiretroviral Therapy – ACTG A5286

Allan R. Tenorio,[1,a] Ellen S. Chan,[4] Ronald J. Bosch,[4] Bernard J. C. Macatangay,[5] Sarah W. Read,[7] Suria Yesmin,[8] Babafemi Taiwo,[3] David M. Margolis,[9] Jeffrey M. Jacobson,[6] Alan L. Landay,[2] and Cara C. Wilson,[10] for the A5286 Team


Rifaximin
No Study Treatment
CD38+ HLA-DR+ CD8+ T Cells, %
0
5
10
15
20
25
30
0
2
4
8
12
Time After Baselines, wk
Individual subjects
Median (IQR) for subjects
Median for HIV-negative controls

RESEARCH ARTICLE

Published September 23, 2019

FOUR WEEKS OF TREATMENT WITH RIFAXIMIN FAILS TO SIGNIFICANTLY ALTER MICROBIAL DIVERSITY IN RECTAL SAMPLES OF HIV-INFECTED IMMUNE NON-RESPONDERS (ACTG A5286) WHICH MAY BE ATTRIBUTED TO RECTAL SWAB USE

AUTHORS

Brett B. Williams[1], Stefan J. Green[2], Ronald J. Bosch[3], Ellen S. Chan[3], Jeffrey M. Jacobson[4], David M. Margolis[5], Phillip Engen[6], Alan L. Landay[7], Cara C. Wilson[8], A5286 protocol team

Williams et al, Pathogens and Immunity 2019

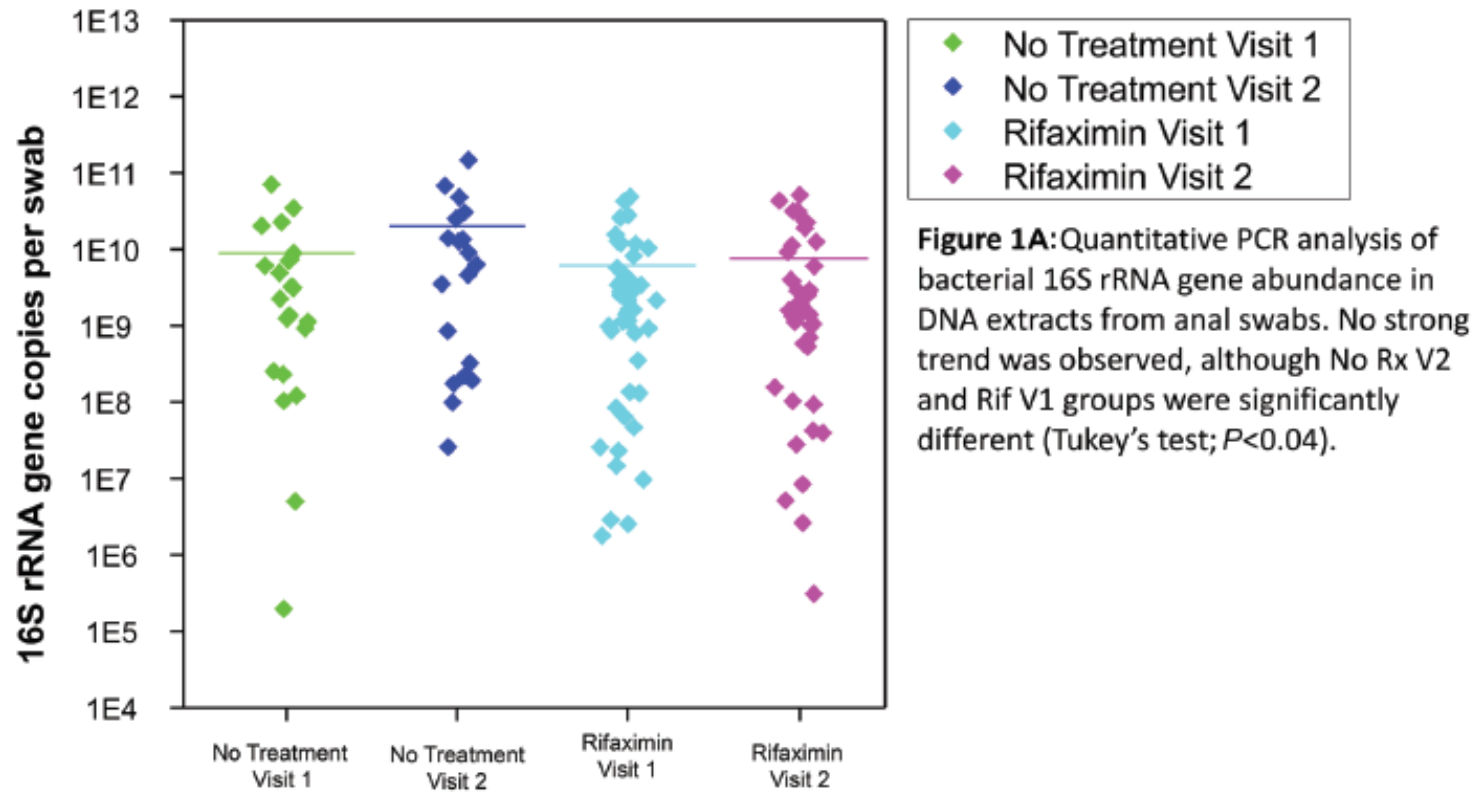


Figure 1A: Quantitative PCR analysis of bacterial 16S rRNA gene abundance in DNA extracts from anal swabs. No strong trend was observed, although No Rx V2 and Rif V1 groups were significantly different (Tukey's test; $P<0.04$).

Figure 1A. Quantitative PCR analysis of bacterial 16S rRNA gene abundance in DNA extracts from anal swabs. No strong trend was observed, although no-treatment visit 2 and Rifaximin visit 1 groups were significantly different (Tukey's test; $P < 0.04$).

Williams et al, Pathogens and Immunity 2019

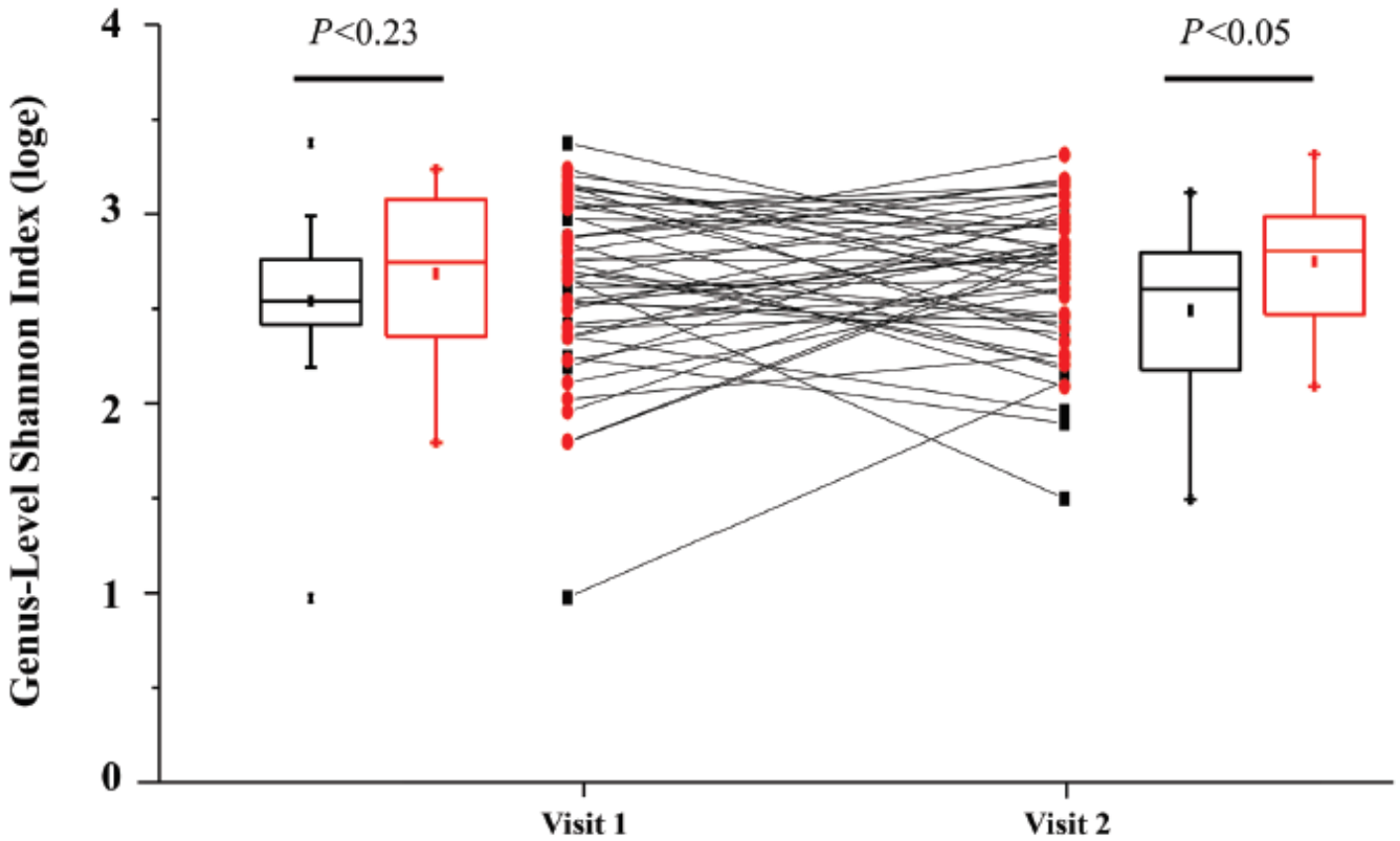


Figure 1B. Change in fecal microbial diversity between visit 1 (before treatment) and visit 2 (after treatment) for individuals taking rifaximin (red circles) and for individuals taking no study treatment (black squares). No significant difference in Shannon Index between treatment groups was observed at baseline (visit 1; Mann-Whitney U-test), but a significant difference was observed at visit 2.

Williams et al, Pathogens and Immunity 2019

Signal Transduction and Targeted Therapy

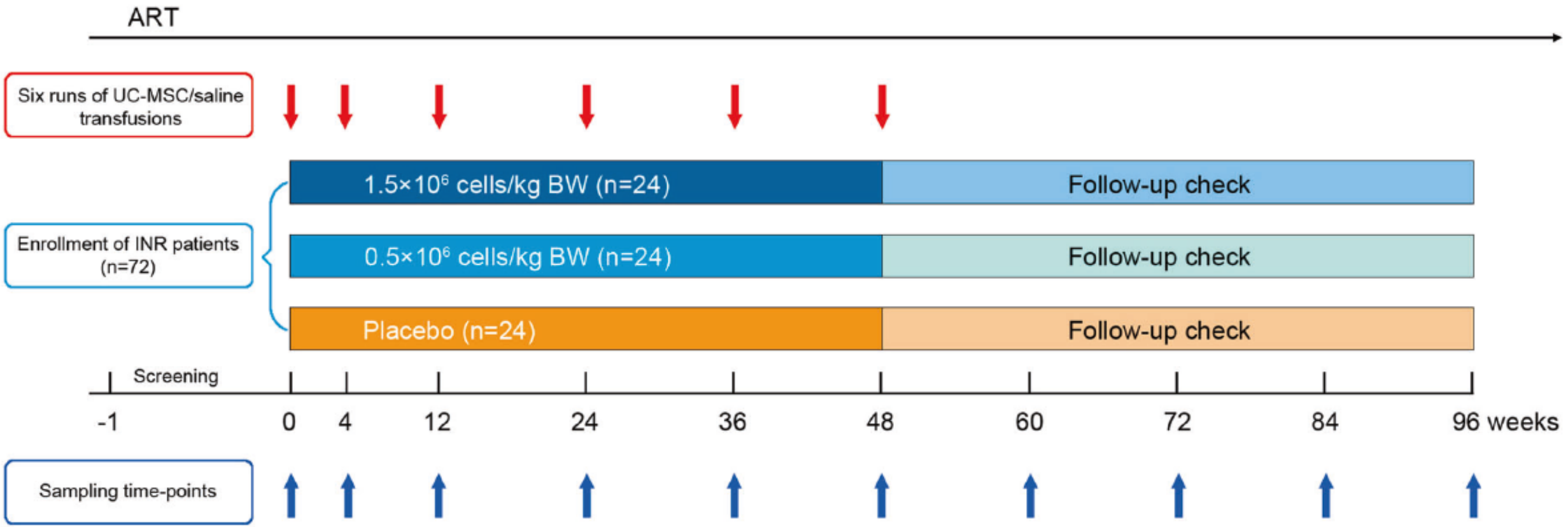
www.nature.com/sigtrans

ARTICLE OPEN

Human umbilical cord mesenchymal stem cell transfusion in immune non-responders with AIDS: a multicenter randomized controlled trial

Lifeng Wang[1], Zheng Zhang[2], Ruonan Xu[1], Xicheng Wang[3], Zhanjun Shu[4], Xiejie Chen[5], Siyu Wang[1], Jiaye Liu[1], Yuanyuan Li[1], Li Wang[3], Mi Zhang[3], Wei Yang[4], Ying Wang[4], Huihuang Huang[1], Bo Tu[1], Zhiwei Liang[5], Linghua Li[5], Jingxin Li[6], Yuying Hou[1], Ming Shi[1] and Fu-Sheng Wang[1]

Wang et al, Signal Transduction and Targeted Therapy 2021



Wang et al, Signal Transduction and Targeted Therapy 2021

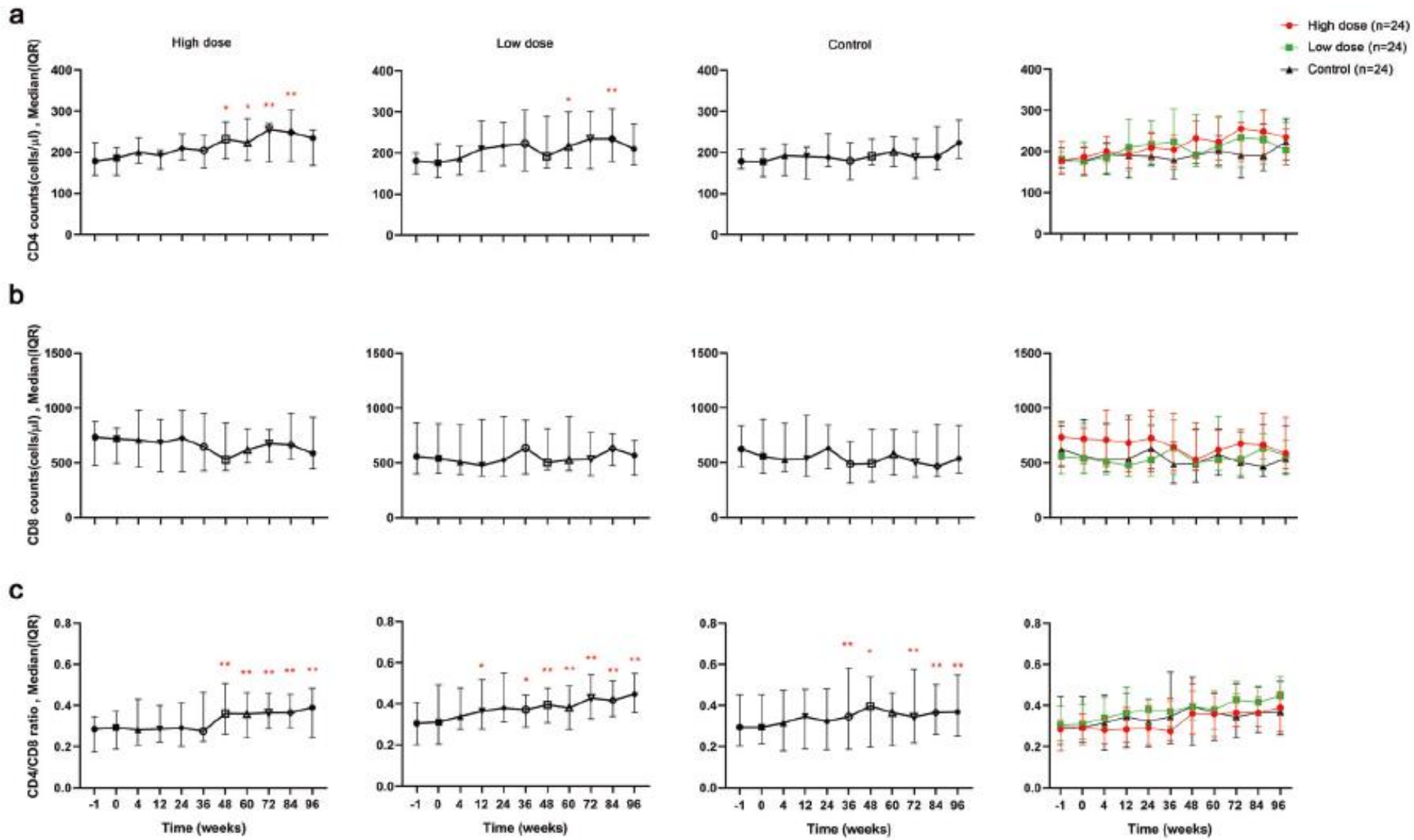


Fig. 2 Longitudinal changes of peripheral CD4 counts, CD8 counts, and CD4/CD8 ratios according to treatment group. **a** CD4 counts; **b** CD8 counts; **c** CD4/CD8 ratios. $^{*}P < 0.05$; $^{**}P < 0.01$

Wang et al, Signal Transduction and Targeted Therapy 2021

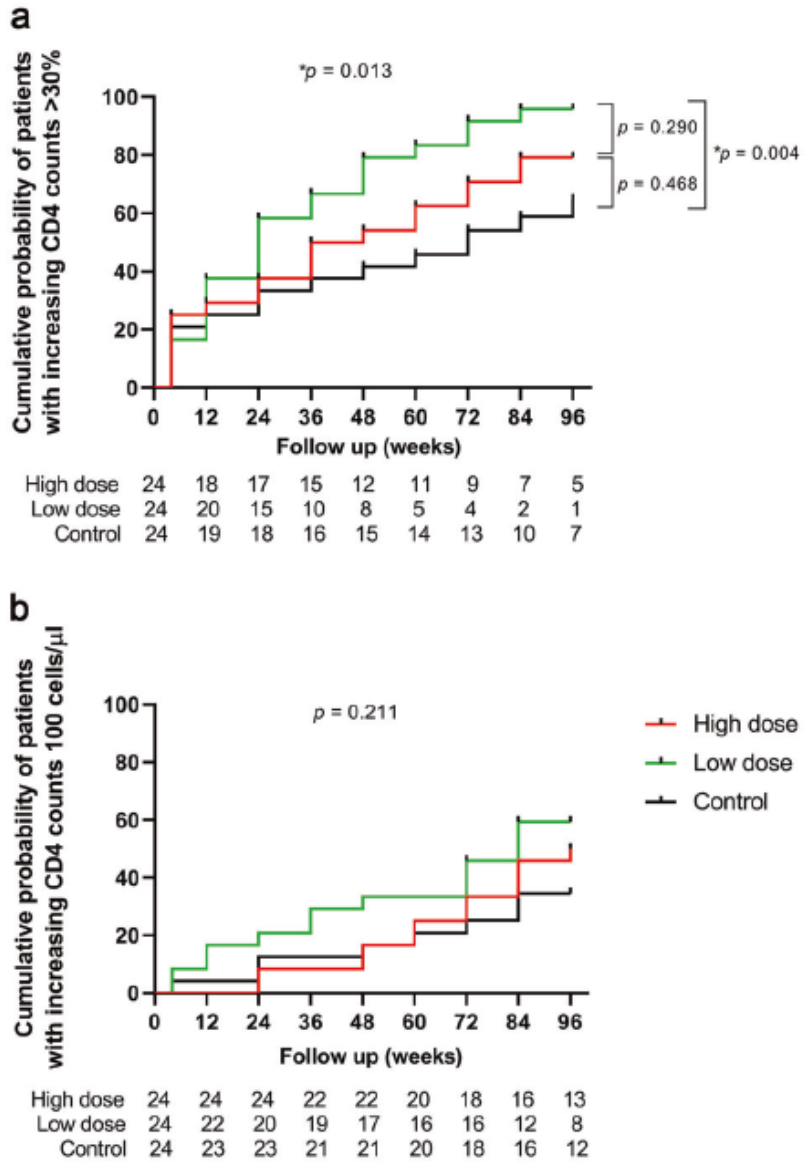


Fig. 3 The cumulative probability of patients with an immunological response. Analyses of the cumulative probability of patients whose CD4 counts increased > 30% (**a**) or (**b**) >100 cells/μL compared with baseline

Wang et al, Signal Transduction and Targeted Therapy 2021

Chinese Medical Journal®

Safety and efficacy of allogeneic natural killer cell immunotherapy on human immunodeficiency virus type 1 immunological non-responders: a brief report

Huan Xia[1], Yin Wang[2], Hua-Li Sun[3], Li-Ying Gao[1], Yu Cao[4], Silvere D. Zaongo[1], Rong-Nan Zeng[4], Hao Wu[5], Ming-Jie Zhang[6], Ping Ma[1]

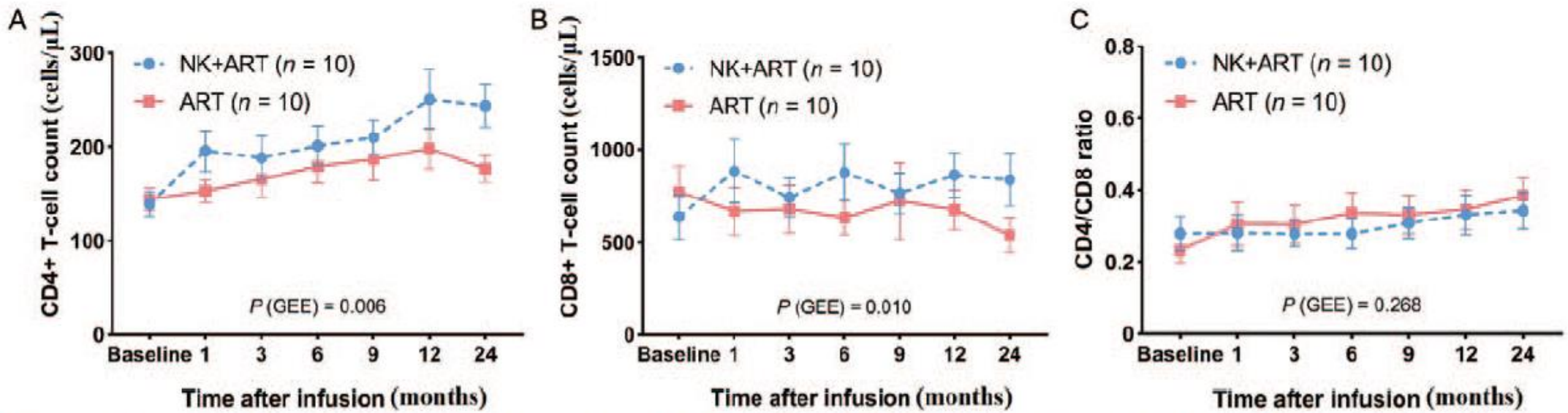


Figure 1: Evolution of the considered markers throughout the follow-up. Mean $CD4^+$ T-cell count (A), $CD8^+$ T-cell count (B), and CD4/CD8 ratio (C) progressions in the NK + ART group *vs.* ART group. ART: Antiretroviral therapy; GEE: Generalized estimating equations; NK: Natural killer cell therapy.

OPEN ACCESS Freely available online

PLOS ONE

Maraviroc as Intensification Strategy in HIV-1 Positive Patients with Deficient Immunological Response: an Italian Randomized Clinical Trial

Stefano Rusconi[1*], Paola Vitiello[1,6], Fulvio Adorni[2], Elisa Colella[1], Emanuele Focà[3], Amedeo Capetti[4], Paola Meraviglia[5], Clara Abeli[6], Stefano Bonora[7], Marco D'Annunzio[8], Antonio Di Biagio[9], Massimo Di Pietro[10], Luca Butini[11], Giancarlo Orofino[12], Manuela Colafigli[13], Gabriella d'Ettorre[14], Daniela Francisci[15], Giustino Parruti[16], Alessandro Soria[17], Anna Rita Buonomini[18], Chiara Tommasi[19], Silvia Mosti[20], Francesca Bai[21], Silvia Di Nardo Stuppino[1], Manuela Morosi[1], Marco Montano[18], Pamela Tau[1], Esther Merlini[21], Giulia Marchetti[21]

Results: By W48 both groups displayed a CD4 increase without a significant inter-group difference. A statistically significant change in CD8 favored patients in arm HAART+maraviroc *versus* HAART at W12 (p=.009) and W48 (p=.025). The CD4>200/μL and CD4>200/μL + CD4 gain ≥25% end-points were not satisfied at W12 (p=.24 and p=.619) nor at W48 (p=.076 and p=.236). Patients continuing HAART displayed no major changes in parameters of T-cell homeostasis and activation. Maraviroc-receiving patients experienced a significant rise in circulating IL-7 by W48 (p=.01), and a trend in temporary reduction in activated HLA-DR+CD38+CD4+ by W12 (p=.06) that was not maintained at W48.

frontiers in Immunology

SYSTEMATIC REVIEW
published: 17 February 2021
doi: 10.3389/fimmu.2021.632119

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Adjunct Therapy for CD4+ T-Cell Recovery, Inflammation and Immune Activation in People Living With HIV: A Systematic Review and Meta-Analysis

OPEN ACCESS

Edited by:
Serge Benichou,

Yang Zhang[1,2,3†], Taiyi Jiang[1†], Aixin Li[1†], Zhen Li[1,2], Jianhua Hou[1,2], Meixia Gao[1], Xiaojie Huang[1], Bin Su[1,2], Hao Wu[1,2], Tong Zhang[1,2*] and Wei Jiang[3,4*]*

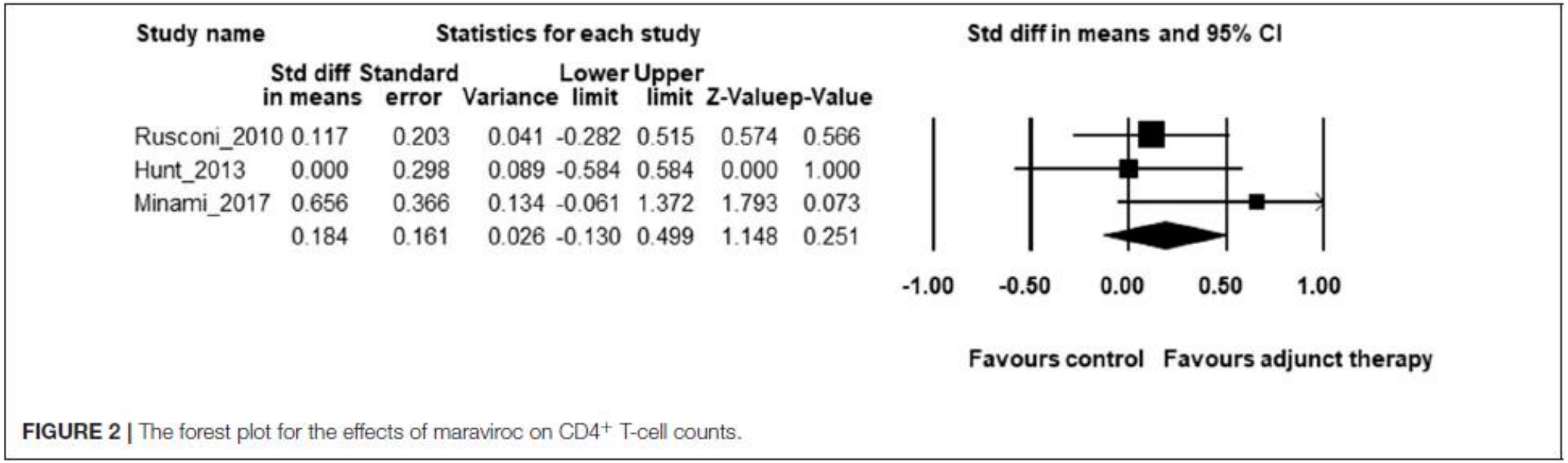


FIGURE 2 | The forest plot for the effects of maraviroc on CD4$^+$ T-cell counts.

CONCLUSIONS

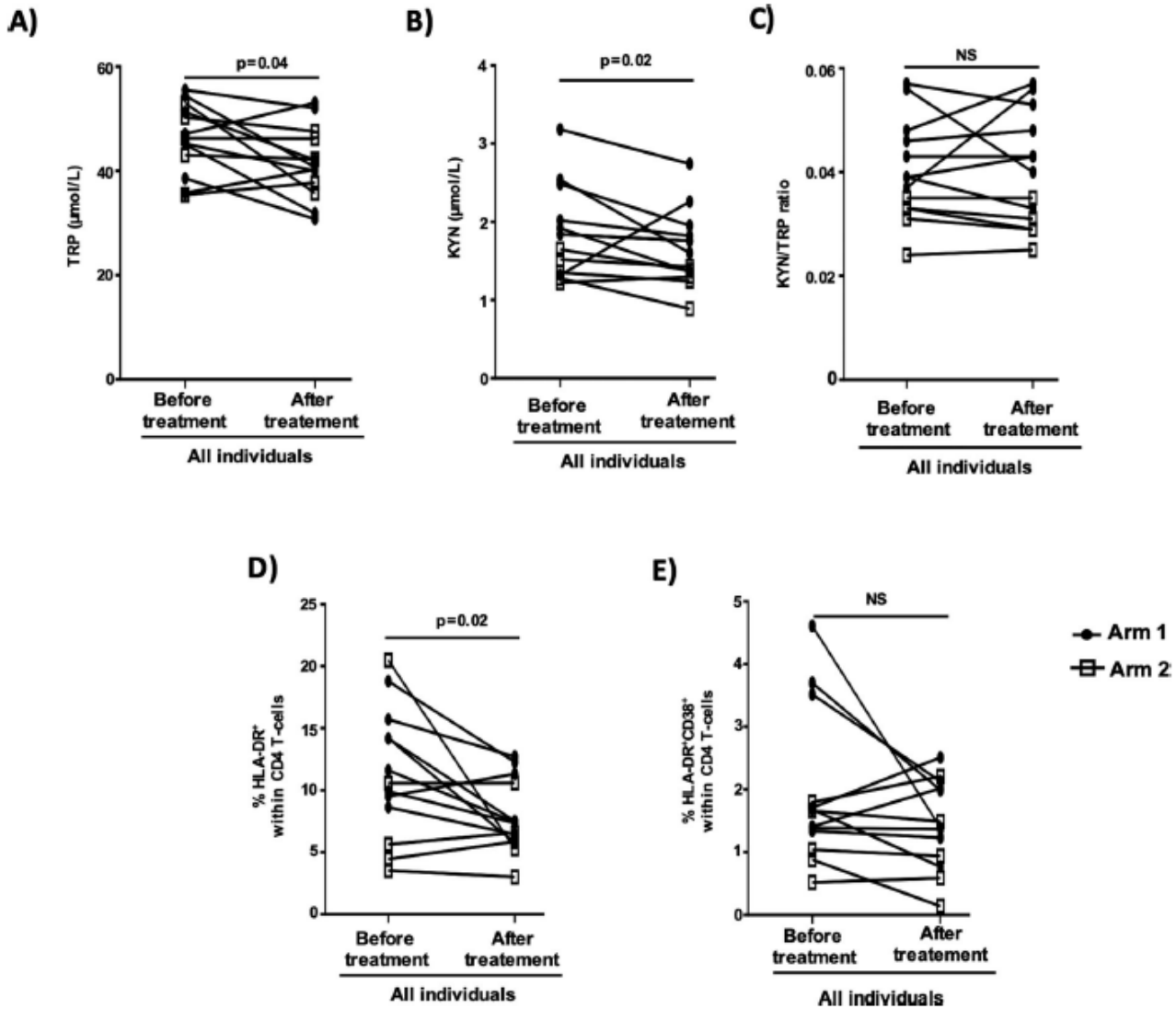
To date, there are no safe and effective medications specific to improving CD4$^+$ T-cell reconstitution. There are still

Zhang et al, Frontiers Immunol 2021

Impact of extended-release niacin on immune activation in HIV-infected immunological non-responders on effective antiretroviral therapy

Bertrand Lebouché[1,2,3,4], Alexis Yero[5], Tao Shi[5], Omar Farnos[5], Joel Singer[6], Ido Kema[7], Cecilia T. Costiniuk[1,2,8], Réjean Thomas[9], Marie-Josée Brouillette[1,2,4,10], Kim Engler[4], Jean-Pierre Routy[1,2], Mohammad-Ali Jenabian[5,8] and for the CTN PTo06 Study Group

HIV Research & Clinical Practice 2020 VOL. 21 NO. 6



Conclusions: Although ER-niacin combined with ART was well-tolerated among immune non-responders and decreased plasma lipids, it did not improve systemic inflammation, Kyn/Trp ratio, and CD4 cell recovery. Overall, ER-niacin was not effective to overcome chronic inflammation in PLWH.

New Microbiologica, 45, 3, 155-172 , 2022, ISSN 1121-7138

REVIEW

Failure of CD4+ T-cell Recovery upon Virally-Effective cART: an Enduring Gap in the Understanding of HIV+ Immunological non-Responders

Valeria Bono, Matteo Augello, Camilla Tincati, Giulia Marchetti

Clinic of Infectious Diseases and Tropical Medicine, San Paolo Hospital, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Italy

Table 1 - *Overview of the major studies evaluating adjuvant therapeutic approaches to enhance CD4+ T-cells recovery in immunological non-responders.*

Reference (year)	*Design*	*Population (study arms)*	*Therapy*	*Duration (follow-up)*	*Main findings*
Maraviroc					
Rusconi *et al.* (2013)	RCT	97 INR pts (47 *vs* 50)	cART ± maraviroc	48 wks (48 wks)	No advantage in CD4 T-cell recovery; expansion of CD8 T-cell counts and activation (CD38+HLA-DR+); rise in plasma IL-7 and IL-7R expression on CD4 T cells
Hunt *et al.* (2013)	RCT	45 INR pts (23 *vs* 22)	cART + maraviroc or placebo	24 wks (36 wks)	No increase in CD4 T-cell count; rise in activated (CD38+HLA-DR+) CD8 T cells; expansion of activated T cells in rectal tissue
van Lelyveld *et al.* (2015)	RCT	85 INR pts (41 *vs* 44)	cART + maraviroc or placebo	48 wks (48 wks)	No rise in CD4 T-cell count; no changes in T-cell activation/proliferation (CD38+HLA-DR+/Ki-67+) and microbial translocation (sCD14); reduction of apoptotic (annexin-V+) T cells
Minami *et al.* (2017)	OS	32 INR pts (18 *vs* 14)	cART ± maraviroc	24 wks (24 wks)	Increase in CD4 T-cell count (>25%) in 12/18 pts (MVC-responders); decreased IFN-γ mRNA in CD4 T cells, especially in MVC-responders

Bono et al, New Microbiol 2022

IL-2					
Marchetti *et al.* (2002)	RCT	22 INR pts (12 *vs* 10)	cART ± IL-2 (sc)	10 wks (48 wks)	Increase in total, naïve (CD45RA+CD62L+) and memory (CD45RA-) CD4 T cells; rise in Th1 (CD4+CD7+) cells; increase of CD8 T cells; transient increase of NK cells; rise in plasma IL-7; no changes in plasma HIV-RNA
Arnó *et al.* (1999)	RCT	25 INR pts (13 *vs* 12)	cART ± IL-2 (sc)	24 wks (24 wks)	Increase of total CD4 T cells; early rise of memory (CD45RO+) CD4 T cells; slow but sustained increase of naïve (CD45RA+) CD4 T cells; no changes in plasma HIV-RNA and viral reservoir (proviral DNA)
Katlama *et al.* (2002)	RCT	70 INR pts (34 *vs* 36)	cART ± IL-2 (sc)	24 wks (24 wks)	Increase in total, naïve (CD45RA+CD62L+) and memory (CD45RO+) CD4 T cells count; no changes in CD8 T cells count; no reduction in activation (CD38+/HLA-DR+/CD28+/CD95+) of CD4 and CD8 T cells; no increase in antigen-specific CD4 T-cell responses
Abrams *et al.* (2009)	RCT	SILCAAT: 1695 INR pts (849 *vs* 846) ESPRIT: 4111 IR pts (2071 *vs* 2040)	cART ± IL-2 (sc)	48 wks of induction (7-8 yrs)	Substantial and sustained increase in CD4 T cells count, but no clinical benefit (as measured by the reduction in the risk of opportunistic disease, death from any cause or potentially threatening events requiring medical intervention) in both INRs and IRs

Bono et al, New Microbiol 2022

Reference (year)	*Design*	*Population (study arms)*	*Therapy*	*Duration (follow-up)*	*Main findings*
IL-7					
Lévy *et al.* (2012)	RCT	32 INR pts (26 *vs* 6)	cART + IL-7 or placebo (sc)	2 wks (52 wks)	Brisk and durable increase of CD4 and CD8 T cells (naïve and central memory); early but transient increase of cycling (Ki-67+) CD4 and CD8 T cells (naïve, central memory and effector memory); no changes in T-cell activation (CD38+HLA-DR+); reduction in exhausted (PD-1+) CD4 and CD8 T cells; increased thymic output and TCR repertoire
Thiébaut *et al.* (2016)	saCT RCT	INSPIRE 2: 23 INR pts INSPIRE 3: 88 INR pts (64 *vs* 24)	INSPIRE 2: cART + IL-7 (sc) INSPIRE 3: cART ± IL-7 (sc)	12 wks of induction (96 wks)	Increase of CD4 T cells (naïve and central memory); CD4 T-cell count >500/μL for >63% of the follow-up time in 50% of treated pts; no changes in CRP and D-dimer

Bono et al, New Microbiol 2022

Probiotics					
Meyer-Myklestad *et al.* (2022)	saCT	20 INR pts	cART + IDOFORM® Travel*	8 wks (10 wks)	No changes in CD4 T cells frequencies, activation (CD38+HLA-DR+) and exhaustion (PD-1+TIGIT+) in peripheral blood; no changes in plasma HIV-RNA and soluble markers of inflammation (CRP, IL-6, IL-18, D-dimer), gut barrier damage (I-FABP, REG3α, zonulin), microbial translocation (LPS, LBP, sCD14, sCD163); non changes in CD4 and CD8 T cells frequencies, activation and exhaustion in ileum/colon mucosa; increased microbiota alpha diversity, increased abundance of *Bifidobacterium* spp. and reduction in IL-22+ CD4 T cells in ileum but not colon mucosa
Rousseau *et al.* (2022)	RCT	29 INR pts (19 *vs* 10)	cART + DSFP° or placebo	48 wks (48 wks)	No changes in CD4 and CD8 T-cell counts; increase of CD4 T-cell activation (CD38+HLA-DR+); no reduction in CD8 T-cell activation; no changes in markers of inflammation (CRP, IFN-γ, IL-6, TNF-α, D-dimer, sVCAM-1), gut permeability (urine lactulose/mannitol ratio) and microbial translocation (sCD14)

Bono et al, New Microbiol 2022

Reference (year)	*Design*	*Population (study arms)*	*Therapy*	*Duration (follow-up)*	*Main findings*
Stem cell therapy					
Zhang *et al.* (2013)	RCT	13 INR pts (7 *vs* 6)	cART + hUC-MSCs or placebo (iv)	8 wks (48 wks)	Increase of circulating naïve (CD45RA+CD27+) and central memory (CD45RA-CD27+) CD4 T cells; increase of CD127+ CD4 T cells, RTE (CD31+) CD4 T cells, Treg cells (CD25+CD127-CD4+); no changes in frequencies of CD8 T cells, B cells, NK cells, NKT cells, DCs, and γδ T cells; increase of functional IFN-γ+/IL-2+ HIV-specific CD4 T cells; reduction of CD4 and CD8 T cells activation/proliferation/exhaustion (CD38+HLA-DR+/Ki-67+/PD-1+); reduction of systemic inflammation (CRP, IFN-α2, TNF-α, IL-1ra, IL-12p70, IL-6, IFN-γ, IL-9, MIP-1β, IL-8, MCP-1, RANTES) and microbial translocation (LPS)
Wang *et al.* (2021)	RCT	72 INR pts (48 *vs* 24)	cART + hUC-MSCs or placebo (iv)	48 wks (96 wks)	Rise in CD4 T-cell counts with both low-doses and high-doses; no changes in CD8 T-cell counts; no increase of the CD4/CD8 ratio; no HIV load rebounds
Trujillo-Rodríguez *et al.* (2021)	RCT	5 INR pts (interrupted after first single-arm phase)	cART + Ad-MSCs (iv)	20 wks (48 wks)	No increase of CD4 T-cell counts or CD4/CD8 ratio; no reduction of CD4 and CD8 T-cell activation (CD38+HLA-DR+), proliferation (Ki-67+), apoptosis (annexin-V+), exhaustion (PD-1+), senescence (CD57+); no changes in NK cells, Treg cells, DCs, markers of inflammation (CRP, IL-6, TNF-α), microbial translocation (sCD14), and viral reservoir (PBMCs-associated HIV-DNA)

Bono et al, New Microbiol 2022



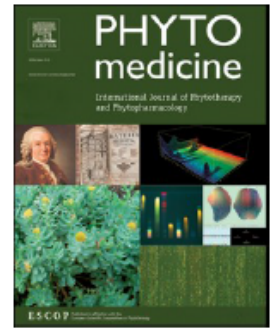
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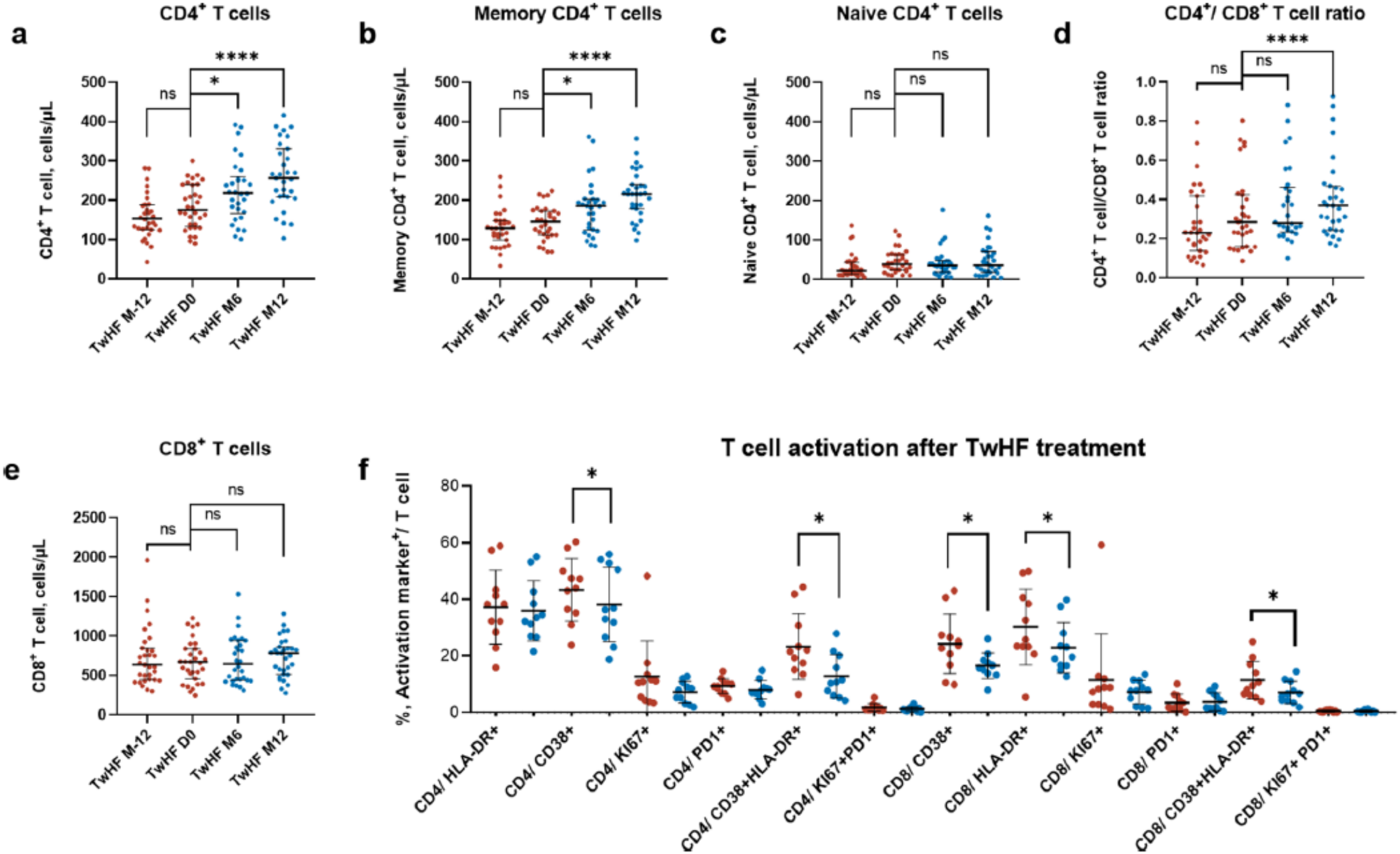


Original Article



Combined multi-omics and network pharmacology approach reveals the role of Tripterygium Wilfordii Hook F in treating HIV immunological non-responders

Xiaosheng Liu [a,b,c], Ling Lin [d], Tingxia Lv [d], Lianfeng Lu [c], Xiaodi Li [c], Yang Han [c], Zhifeng Qiu [c], Xiaoxia Li [c], Yanling Li [c], Xiaojing Song [c], Wei Cao [c], Taisheng Li [a,b,c,*]


a
CD4+ T cells
CD4+ T cell, cells/μL
ns
*
****
TwHF M-12
TwHF D0
TwHF M6
TwHF M12
b
Memory CD4+ T cells
Memory CD4+ T cell, cells/μL
c
Naive CD4+ T cells
Naive CD4+ T cell, cells/μL
d
CD4+/ CD8+ T cell ratio
CD4+ T cell/CD8+ T cell ratio
e
CD8+ T cells
CD8+ T cell, cells/μL
f
T cell activation after TwHF treatment
%, Activation marker+/ T cell
CD4/ HLA-DR+
CD4/ CD38+
CD4/ KI67+
CD4/ PD1+
CD4/ CD38+HLA-DR+
CD4/ KI67+PD1+
CD8/ CD38+
CD8/ HLA-DR+
CD8/ KI67+
CD8/ PD1+
CD8/ CD38+HLA-DR+
CD8/ KI67+ PD1+

(5R)-5-hydroxytriptolide for HIV immunological non-responders receiving ART: a randomized, double-blinded, placebo-controlled phase II study

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Research in context

Evidence before this study

Around 20–30% of treated patients with HIV fail to achieve optimal immune reconstitution and remain at greater risk of morbidity and mortality. We searched PubMed, up to November 25, 2022, for published clinical randomized trials among HIV-infected immunological non-responders (INRs). The search terms used were ("HIV" or "human immunodeficiency virus") AND ("INR" or "immunological non-responder" or "suboptimal CD4 recovery") AND ("clinical trial" or "randomized controlled trial" or "randomised controlled trial"), and produced 17 results. We identified several published clinical trials in HIV-infected INRs, including mesenchymal cell therapy, interleukin-2 (IL-2) therapy, maraviroc, atorvastatin, niacin, artesunate, hyperimmune bovine colostrum (HIBC), probiotics, and traditional Chinese medicines. However, none of these had been proven with efficacy in improving $CD4^+$ T cell recovery and reducing immune activation. Therapeutic approaches to HIV-suppressed INRs remain unsettled.

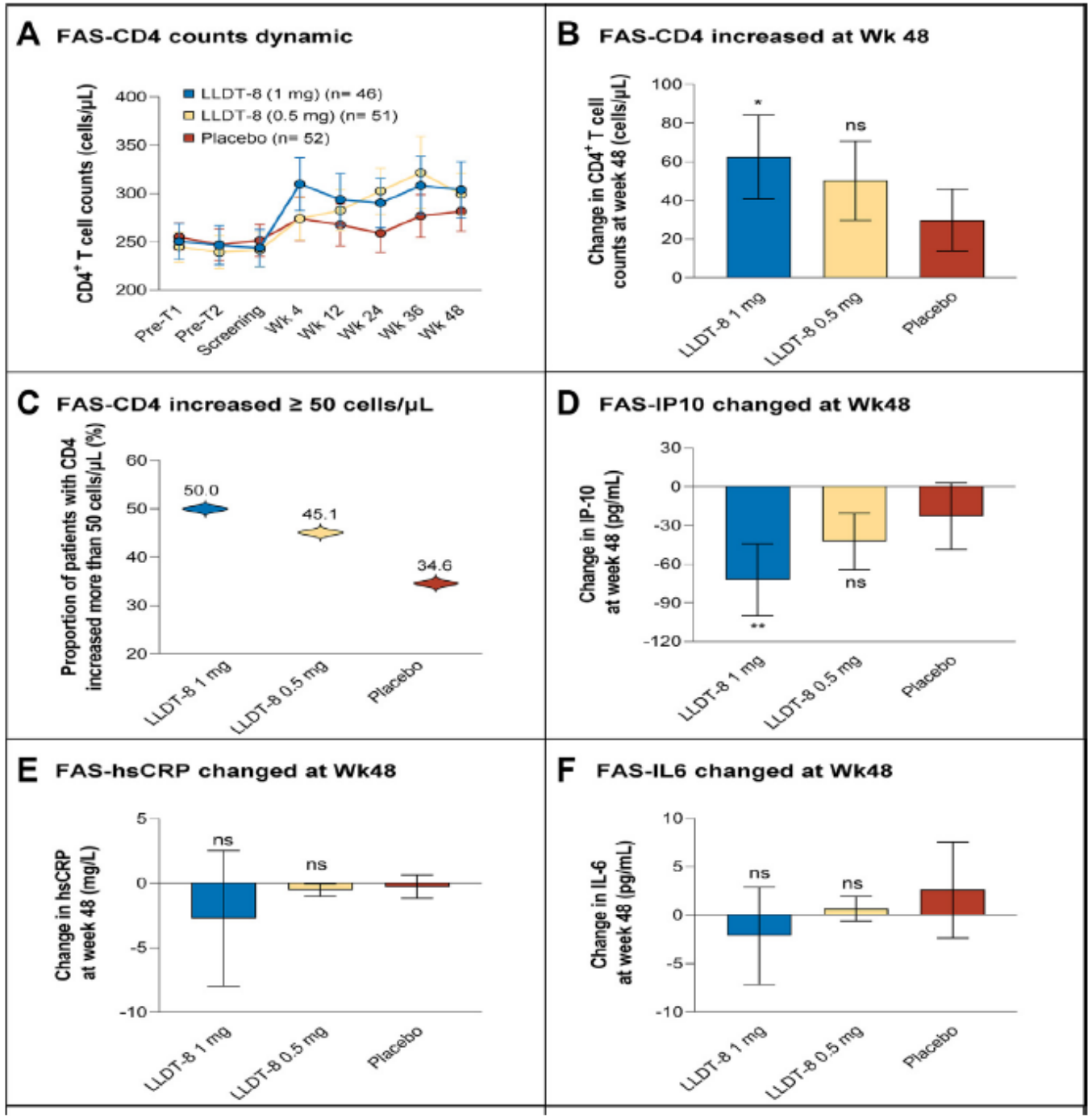
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Characteristics	Total (N = 149)	LLDT-8 1 mg (N = 46)	LLDT-8 0.5 mg (N = 51)	Placebo (N = 52)
Male sex — no. (%)	145 (97.3)	46 (100)	48 (94.1)	51 (98.1)
Age, median (range) — yr	41 (22–64)	41 (28–64)	41 (26–61)	44 (22–64)
Age group — no. (%)				
18–45 yr	91 (61.1)	29 (63.0)	35 (68.6)	27 (51.9)
45–65 yr	58 (38.9)	17 (37.0)	16 (31.4)	25 (48.1)
Ethnicity Han — no. (%)	142 (95.3)	44 (95.7)	48 (94.1)	50 (96.2)
BMI — kg/m^2	22.3 ± 2.5	22.1 ± 2.2	22.5 ± 2.9	22.2 ± 2.4
ART duration, median (range) — yr	6.1 (4.1–14.9)	6.1 (4.1–11.7)	6.1 (4.1–14.9)	6.0 (4.2–10.7)
ART regimens — no. (%)				
NNRTI-based	105 (70.5)	31 (67.4)	39 (76.5)	35 (67.3)
TDF+3TC + EFV	68 (45.6)	19 (41.3)	27 (52.9)	22 (42.3)
PI/r-based	27 (18.1)	12(26.1)	6 (11.8)	9 (17.3)
INSTI-based	17 (11.4)	3 (6.5)	6 (11.8)	8 (15.4)
CD4 lymphocyte count, median (range) — $cells/mm^3$	248 (18–347)	249 (18–343)	243 (87–347)	249 (119–341)
CD4 lymphocyte stratification— no. (%)				
<200 $cells/mm^3$	38 (25.5)	10 (21.7)	15 (29.4)	13 (25.0)
≥200 $cells/mm^3$	111 (74.5)	36 (78.3)	36 (70.6)	39 (75.0)
CD8 lymphocyte count, median (range) — $cells/mm^3$	518 (134–1611)	527 (134–1196)	495 (177–1383)	538 (255–1161)
CD4/CD8 ratio, median (range)	0.45 (0.10–1.61)	0.45 (0.10–1.61)	0.47 (0.21–1.27)	0.45 (0.15–1.26)

[a]The analysis set for participants who underwent randomization in this study. Percentages may not total 100 because of rounding. Plus-minus values are means ± SD. BMI denotes body mass index; SD, standard deviation; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; PI/r, ritonavir-boosted protease inhibitor; INSTI, integrase strand transfer inhibitor.

Table 1: **Characteristics of the participants at baseline, according to full analysis set[a].**

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In conclusione

• IL-2	☒ no
• eradicare Hp e HCV	☑ sì (lo faremmo comunque)
• rifaximina	☒ no
• maraviroc	☒ no
• UC-MSC	☒ no
• ER-niacina	☒ no
• IL-7	☒ forse (impatto clinico?)
• LLDT-8	☒ forse (impatto clinico?)

E quindi? (opinioni personali)

- Il tempo è galantuomo
- Test early, treat early
- Il vero problema? Mortalità in AIDS avanzato che non immunoricostituisce (micobatteriosi atipica)
- Studiare checkpoint inhibitors (anti-PD1/PDL1)?