

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



Doubling dolutegravir dosage reduces the viral reservoir in ART-treated people with HIV

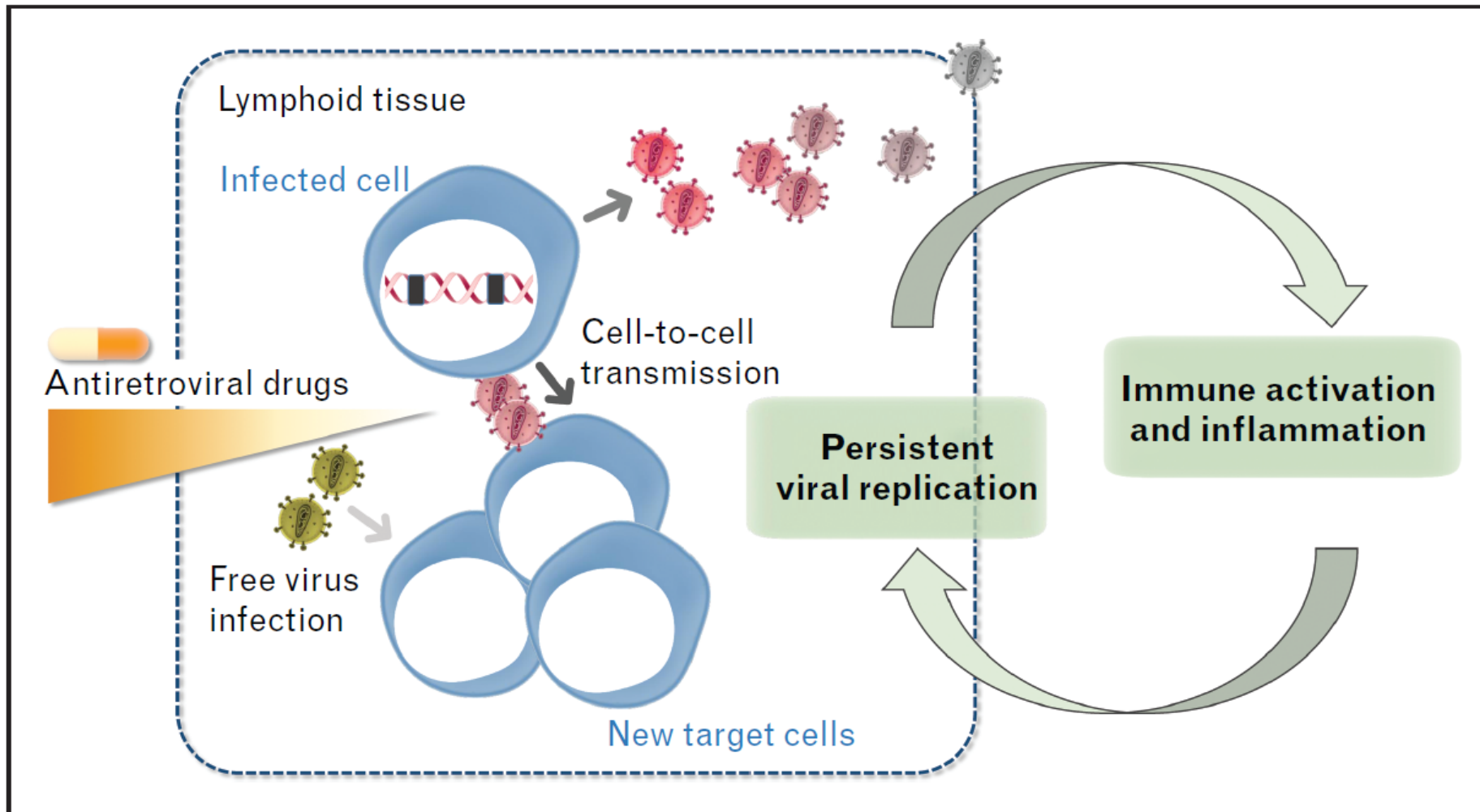
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The Netherlands*

CONFLICTS OF INTEREST

None

Does ART always stop all new infections?



Martinez-Picado and Deeks, Curr Opin HIV AIDS 2016

YES

NO

SCIENCE ADVANCES | RESEARCH ARTICLE

DISEASES AND DISORDERS

No evidence of ongoing HIV replication or compartmentalization in tissues during combination antiretroviral therapy: Implications for HIV eradication

G. Bozzi^{1,2*}, F. R. Simonetti^{1,2*†}, S. A. Watters^{1,3*}, E. M. Anderson¹, M. Gouzoulis¹, M. F. Kearney¹, P. Rote¹, C. Lange¹, W. Shao⁴, R. Gorelick⁵, B. Fullmer⁵, S. Kumar⁶, S. Wank⁶, S. Hewitt⁷, D. E. Kleiner^{7,8}, J. Hattori¹, M. J. Bale¹, S. Hill¹, J. Bell¹, C. Rehm⁹, Z. Grossman¹, R. Yarchoan¹⁰, T. Uldrick¹⁰, F. Maldarelli^{1‡}

The Journal of Clinical Investigation

RESEARCH ARTICLE

No evidence of HIV replication in children on antiretroviral therapy

Gert U. Van Zyl,¹ Mary Grace Katusiime,¹ Ann Wiegand,² William R. McManus,² Michael J. Bale,² Elias K. Halvas,³ Brian Luke,⁴ Valerie F. Boltz,² Jonathan Spindler,² Barbara Laughton,⁵ Susan Engelbrecht,¹ John M. Coffin,⁶ Mark F. Cotton,⁵ Wei Shao,⁴ John W. Mellors,³ and Mary F. Kearney²

OPEN ACCESS Freely available online

 PLOS | PATHOGENS

Lack of Detectable HIV-1 Molecular Evolution during Suppressive Antiretroviral Therapy

Mary F. Kearney^{1*}, Jonathan Spindler¹, Wei Shao², Sloane Yu¹, Elizabeth M. Anderson¹, Angeline O'Shea³, Catherine Rehm³, Carry Poethke¹, Nicholas Kovacs¹, John W. Mellors⁴, John M. Coffin⁵, Frank Maldarelli¹

ARTICLE

doi:10.1038/nature16933

Persistent HIV-1 replication maintains the tissue reservoir during therapy

Ramon Lorenzo-Redondo^{1*}, Helen R. Fryer^{2*}, Trevor Bedford³, Eun-Young Kim¹, John Archer⁴, Sergei L. Kosakovsky Pond^{5†}, Yoon-Seok Chung⁶, Sudhir Penugonda¹, Jeffrey G. Chipman⁷, Courtney V. Fletcher⁸, Timothy W. Schacker⁹, Michael H. Malim¹⁰, Andrew Rambaut¹¹, Ashley T. Haase¹², Angela R. McLean² & Steven M. Wolinsky¹

LETTER

doi:10.1038/nature10347

Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy

Alex Sigal¹, Jocelyn T. Kim^{1,2}, Alejandro B. Balazs¹, Erez Dekel³, Avi Mayo³, Ron Milo⁴ & David Baltimore¹

Modest Nonadherence to Antiretroviral Therapy Promotes Residual HIV-1 Replication in the Absence of Virological Rebound in Plasma

Alexander O. Pasternak,^{1,3} Marijn de Bruin,⁵ Suzanne Jurriaans,² Margreet Bakker,^{1,3} Ben Berkhout,^{1,3} Jan M. Prins,⁴ and Vladimir V. Lukashov^{1,3}

Does ART always stop all new infections?

YES

Reservoir persists by cellular longevity and proliferation and is insensitive to ART

Cure should focus on eradication of reservoir cells

NO

Reservoir may be also continuously replenished by residual replication

If infection of new cells is not completely blocked, some cure strategies might do more harm than good

Improved ART regimens should be part of cure strategies

Increase in 2-Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial

Hiroyu Hatano,¹ Matthew C. Strain,^{4,5} Rebecca Scherzer,^{1,3} Peter Bacchetti,² Deborah Wentworth,⁶ Rebecca Hoh,¹ Jeffrey N. Martin,² Joseph M. McCune,¹ James D. Neaton,⁶ Russell P. Tracy,⁷ Priscilla Y. Hsue,¹ Douglas D. Richman,^{4,5} and Steven G. Deeks¹

Effect of raltegravir-containing intensification on HIV burden and T-cell activation in multiple gut sites of HIV-positive adults on suppressive antiretroviral therapy

Steven A. Yukl^a, Amandeep K. Shergill^a, Kenneth McQuaid^a, Sara Gianella^b, Harry Lampiris^a, C. Bradley Hare^c, Mark Pandori^d, Elizabeth Sinclair^c, Huldrych F. Günthard^b, Marek Fischer^b, Joseph K. Wong^a and Diane V. Havlir^c

Short-Course Raltegravir Intensification Does Not Reduce Persistent Low-Level Viremia in Patients with HIV-1 Suppression during Receipt of Combination Antiretroviral Therapy

D. McMahon,¹ J. Jones,¹ A. Wiegand,² S. J. Gange,³ M. Kearney,² S. Palmer,^{2a} S. McNulty,¹ J. A. Metcalf,⁴ E. Acosta,⁵ C. Rehm,⁴ J. M. Coffin,² J. W. Mellors,¹ and F. Maldarelli²

A Randomized, Controlled Trial of Raltegravir Intensification in Antiretroviral-treated, HIV-infected Patients with a Suboptimal CD4⁺ T Cell Response

Hiroyu Hatano,¹ Timothy L. Hayes,² Viktor Dahl,³ Elizabeth Sinclair,¹ Tzong-Hae Lee,⁴ Rebecca Hoh,¹ Harry Lampiris,^{1,5} Peter W. Hunt,¹ Sarah Palmer,³ Joseph M. McCune,¹ Jeffrey N. Martin,¹ Michael P. Busch,^{1,4} Barbara L. Shacklett,² and Steven G. Deeks¹

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

Maria J Buzón^{1,9}, Marta Massanella^{1,9}, Josep M Llibre², Anna Esteve³, Viktor Dahl⁴, Maria C Puertas¹, Josep M Gatell⁵, Pere Domingo⁶, Roger Paredes^{1,2}, Mark Sharkey⁷, Sarah Palmer⁴, Mario Stevenson⁷, Bonaventura Clotet^{1,2}, Julià Blanco¹ & Javier Martinez-Picado^{1,8}

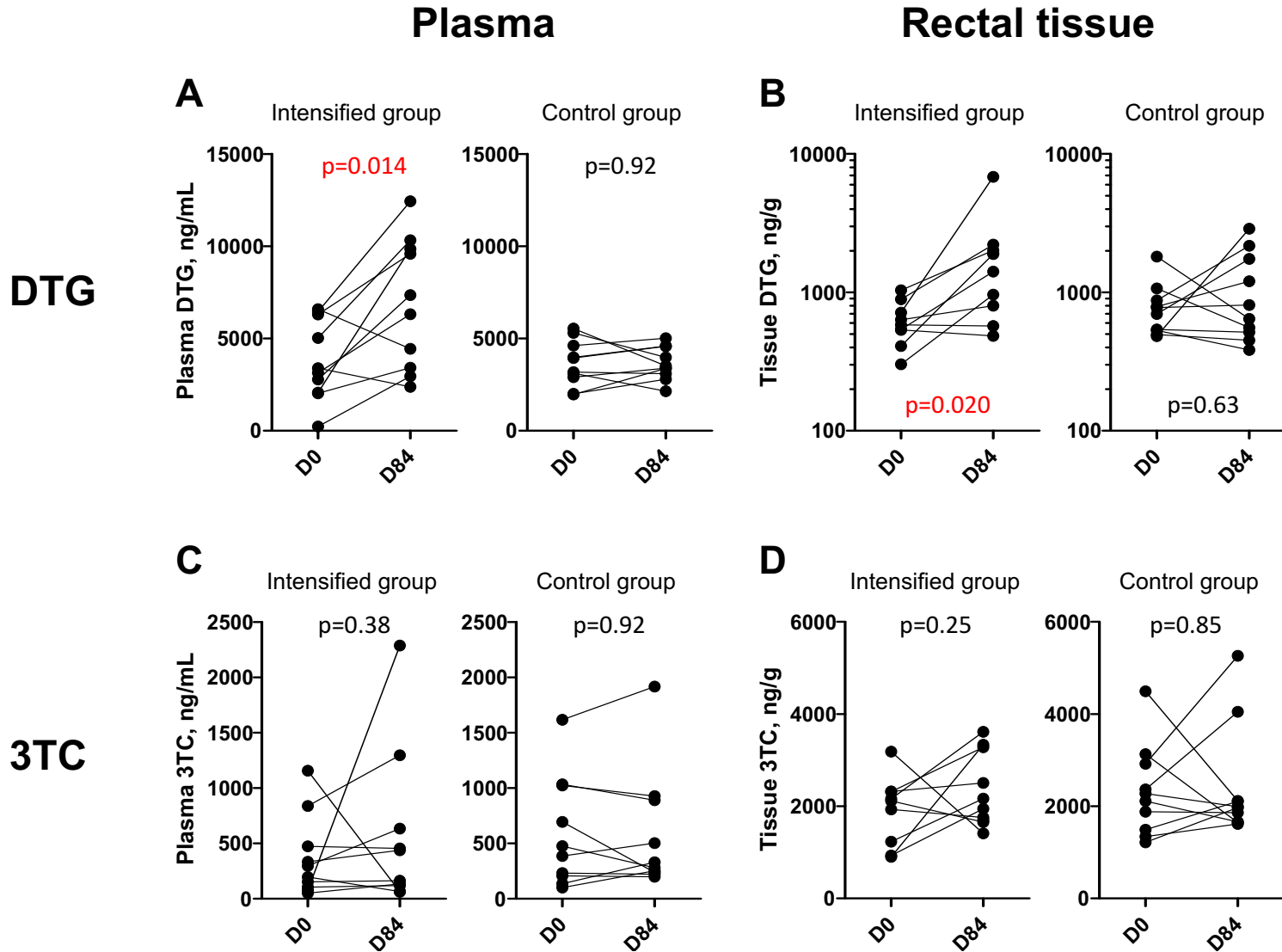
The effect of antiretroviral intensification with dolutegravir on residual virus replication in HIV-infected individuals: a randomised, placebo-controlled, double-blind trial

Thomas A Rasmussen*, James H McMahon*, J Judy Chang, Jennifer Audsley, Ajantha Rhodes, Surekha Tennakoon, Ashanti Dantanarayana, Tim Spelman, Tina Schmidt, Stephen J Kent, Vincent Morcilla, Sarah Palmer, Julian H Elliott, Sharon R Lewin

The Effect of Raltegravir Intensification on Low-level Residual Viremia in HIV-Infected Patients on Antiretroviral Therapy: A Randomized Controlled Trial

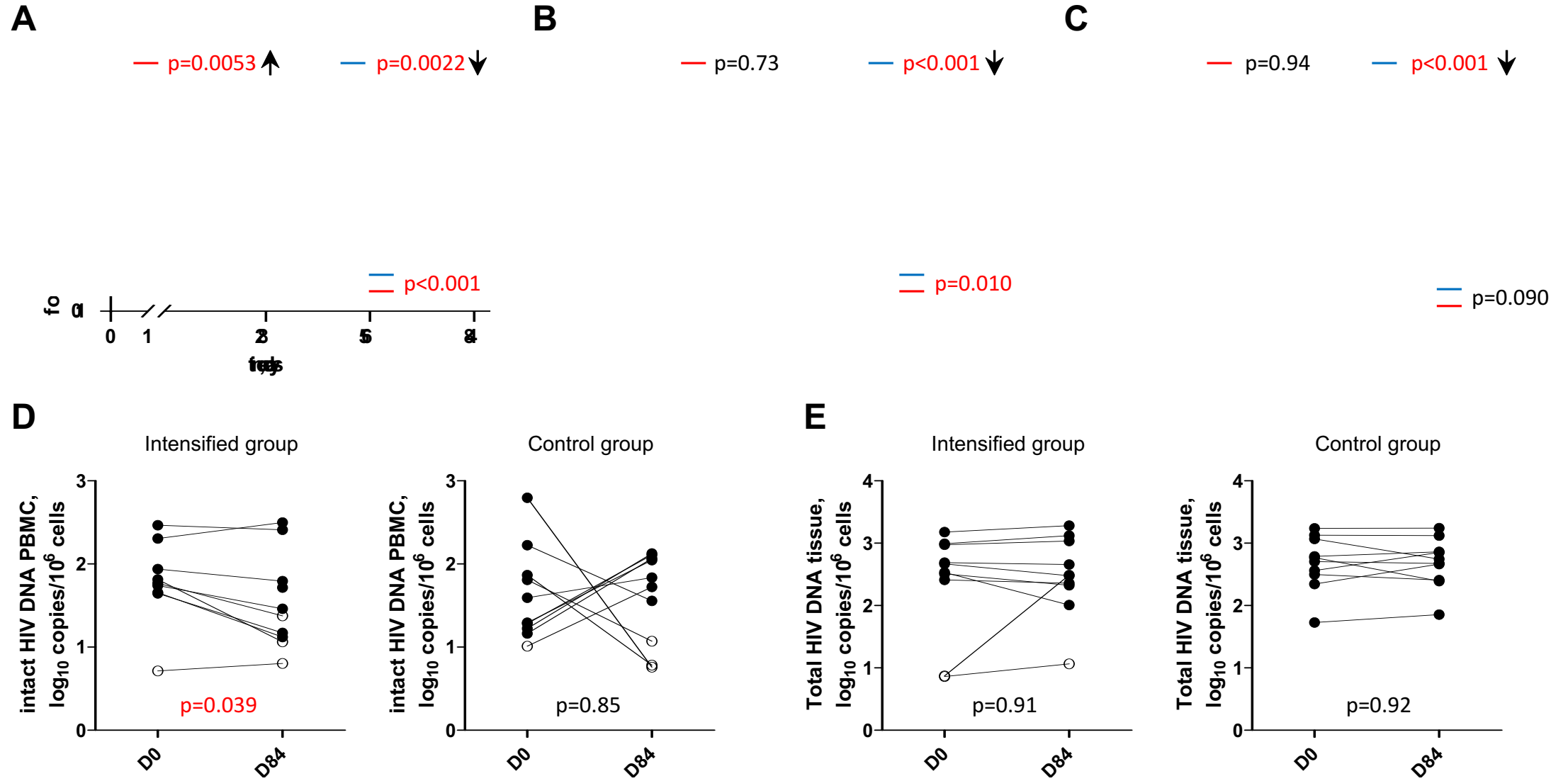
Rajesh T. Gandhi^{1*}, Lu Zheng², Ronald J. Bosch², Ellen S. Chan², David M. Margolis³, Sarah Read⁴, Beatrice Kallungal⁵, Sarah Palmer⁶, Kathy Medvik⁷, Michael M. Lederman⁷, Nadia Alatrakchi⁸, Jeffrey M. Jacobson⁹, Ann Wiegand¹⁰, Mary Kearney¹⁰, John M. Coffin¹¹, John W. Mellors¹², Joseph J. Eron³, on behalf of the AIDS Clinical Trials Group A5244 team[†]

Plasma and rectal tissue concentrations of DTG and 3TC

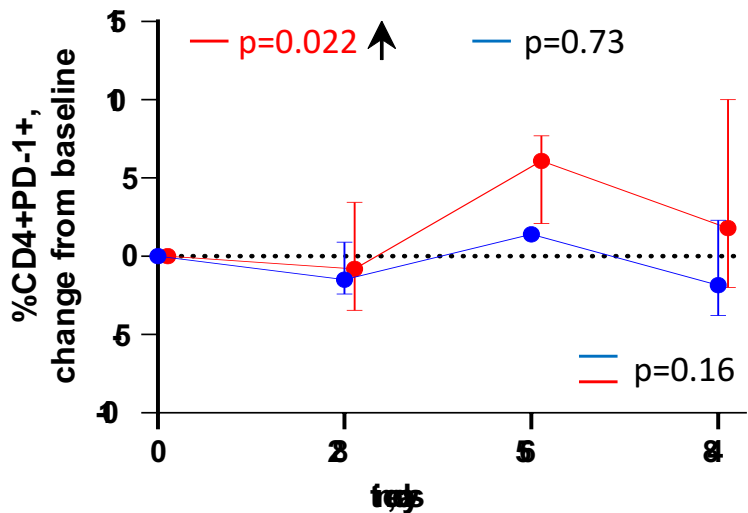


Longitudinal dynamics of HIV reservoir markers

● Intensified group ● Control group



Longitudinal dynamics of cellular markers of immune activation and exhaustion (CD4+ T cells)



p=0.43

p=0.33

p=0.45

p=0.82

● Intensified group

● Control group

p=0.46

p=0.49

p=0.14

p=0.031 ↓

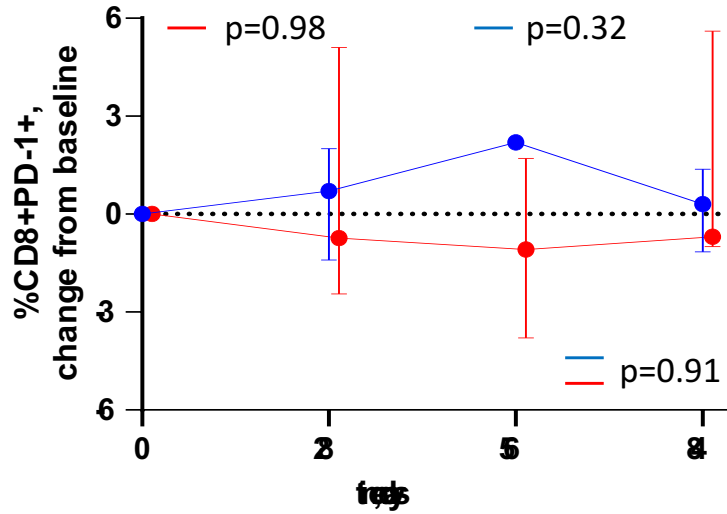
p=0.24

p=0.58

p=0.048

p=0.54

Longitudinal dynamics of cellular markers of immune activation and exhaustion (CD8+ T cells)



— p=0.034 ↓ — p=0.12

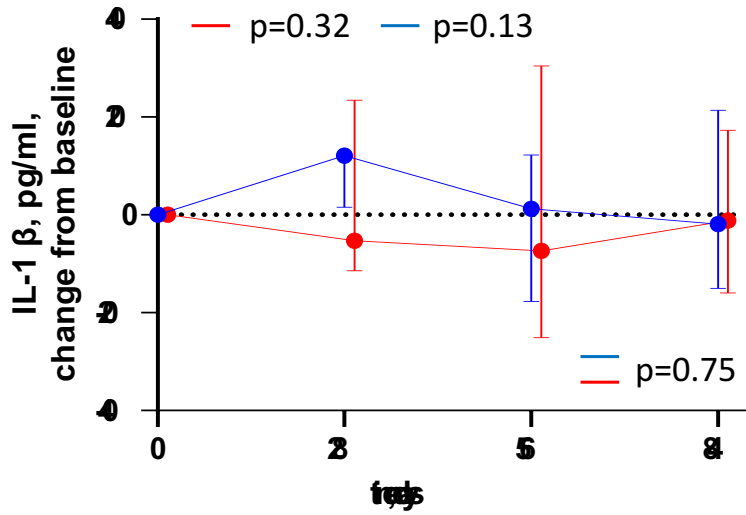
— p=0.13 — p=0.049 ↓

— p=0.090

— p=0.30

— p=0.23 — p=0.44 — p=0.72 — p=0.81
 — p=0.51 — p=0.85
 • Intensified group • Control group

Longitudinal dynamics of inflammatory cytokines (plasma)



— p=0.049 ↑ — p=0.15

— p=0.78 — p=0.11

— p=0.49

— p=0.69

— p=0.77 — p=0.11

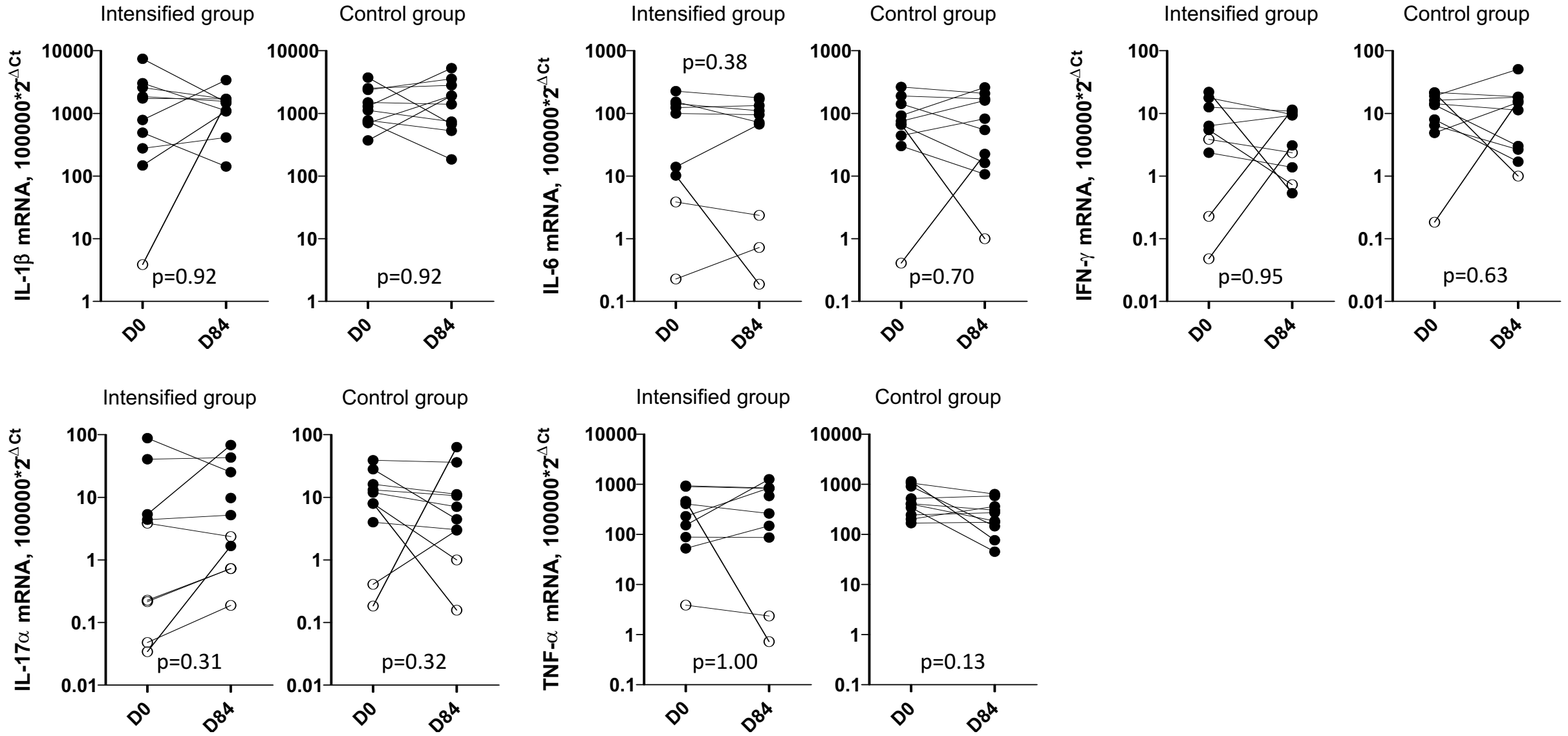
— p=0.94 — p=0.90

● Intensified group ● Control group

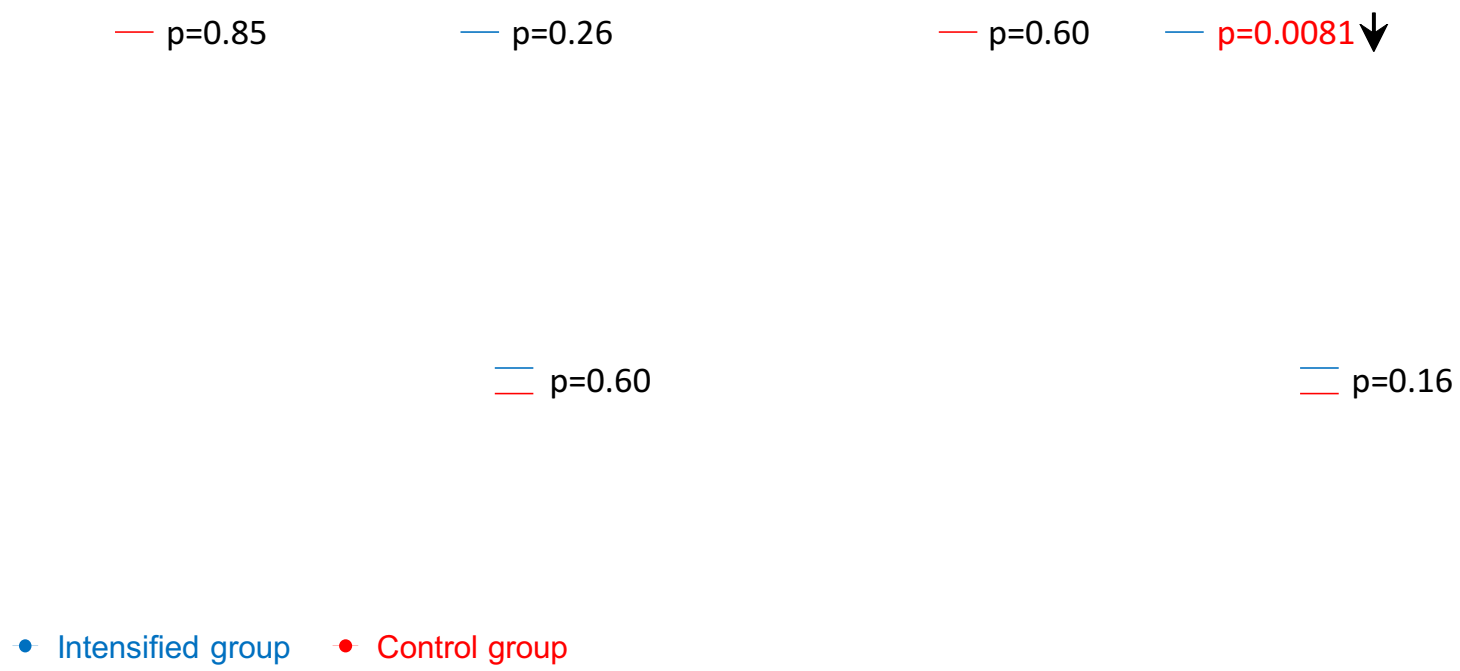
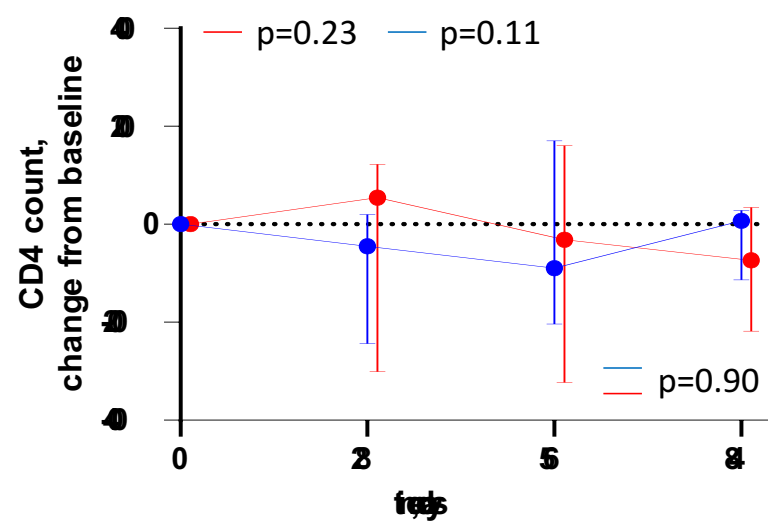
— p=0.68

— p=0.80

Longitudinal dynamics of inflammatory cytokines (rectal tissue)



Longitudinal dynamics of CD4 count, CD8 count, and CD4/CD8 ratio



Conclusions

Significant longitudinal decreases in total HIV DNA, intact HIV DNA, and US HIV RNA in PBMCs, as well as in the US RNA/total DNA ratio, were observed in the intensified group but not in the control group

Intensification also reduced frequencies of CD4+ cells expressing TIGIT, a marker of immune exhaustion, but had no measurable impact on systemic or tissue inflammation

Intensification resulted in a transient reduction in the CD4/CD8 ratio, which returned to baseline by day 84

Our results suggest that the pre-intensification ART regimen may not have been completely suppressive

If confirmed in larger clinical trials, these results could have an impact on the clinical management of people with HIV and curative strategies

Acknowledgements

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