

The Importance of Triple ART in the Long-Term Management of HIV Infection

Sergio Serrano Villar



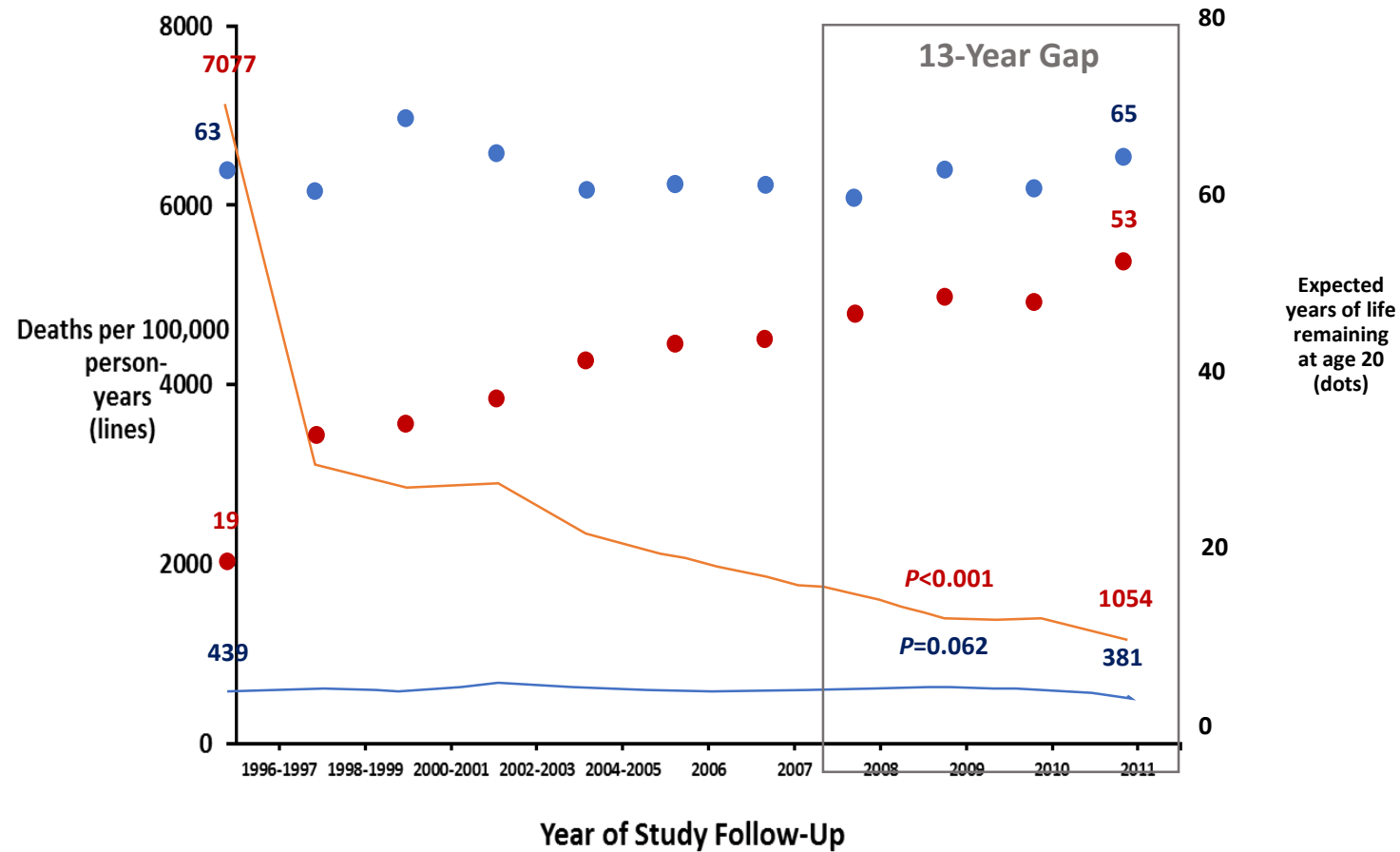
Disclosures

El Dr. Sergio Serrano ha prescrito:

- TAR cuádruple
- TAR triple
- TAR doble
- TAR mono

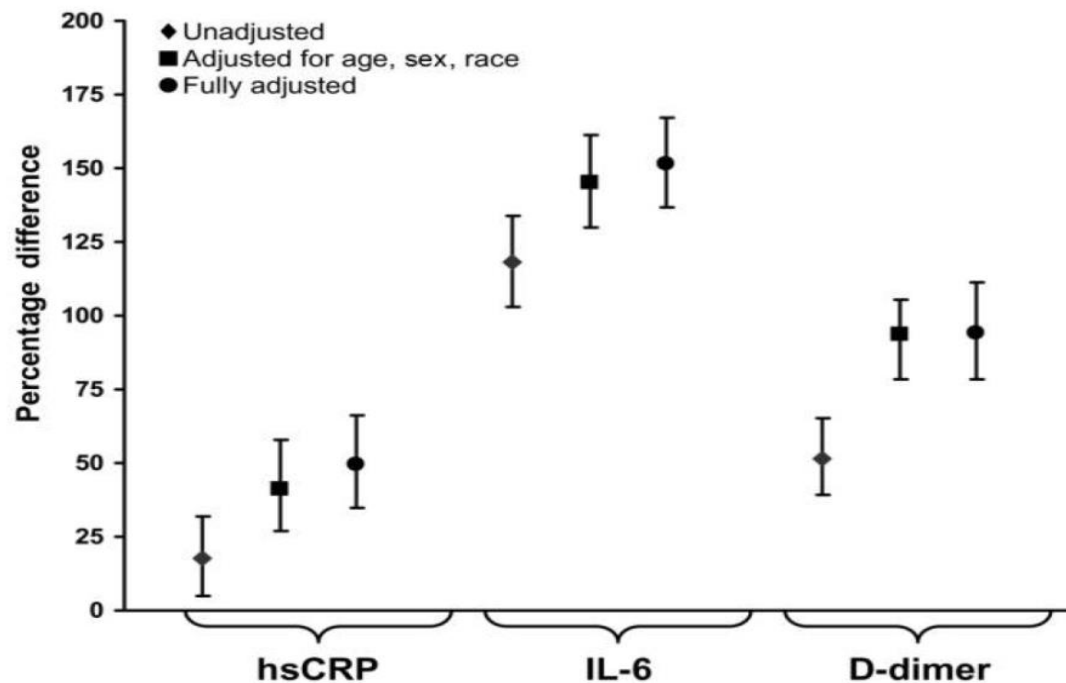
**What is the main
unmet goal of ART?**

Kaiser Permanente HIV Cohort: Narrowing the Gap in Life Expectancy for HIV+ vs HIV-Individuals

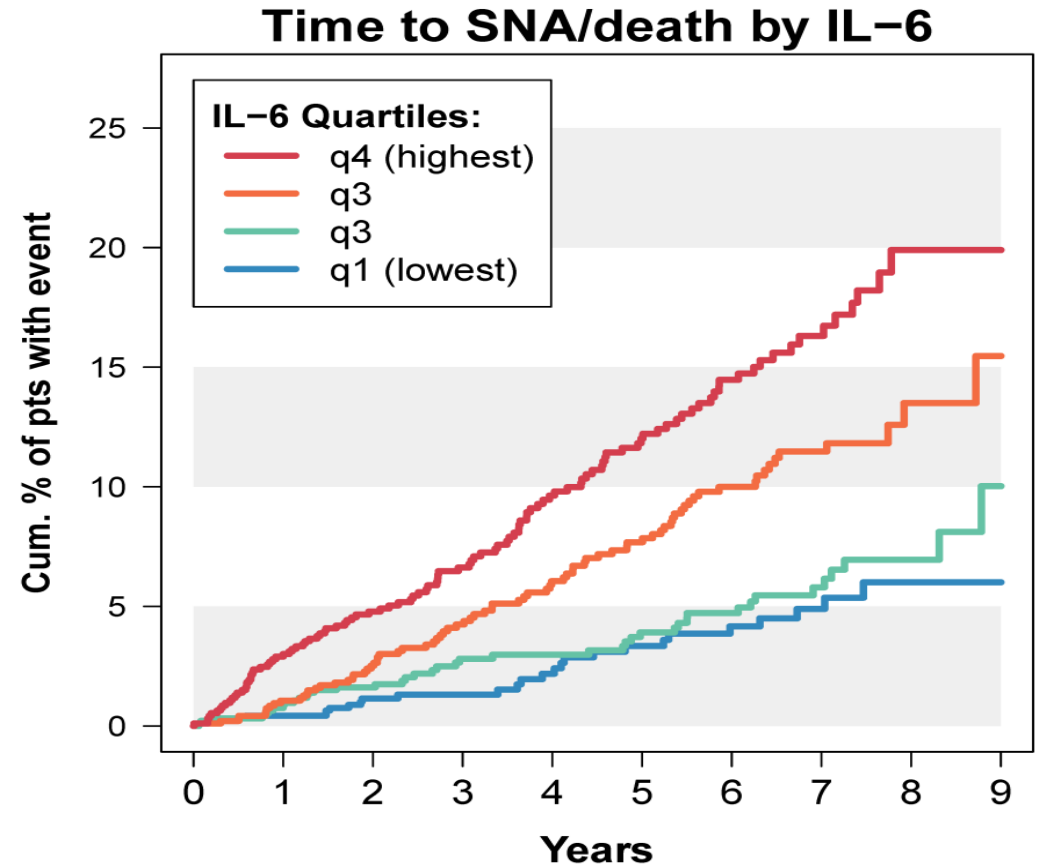


8 year gap with ART initiation at CD4 $\geq$ 500. Life expectancy ↓ Blacks & IVDU. ↓ Hispanics
Gap narrowed if no hepatitis, drug/alcohol, or smoking

The Increase of Inflammatory Biomarkers is only Moderate but the Impact on Long-Term Mortality is Strong

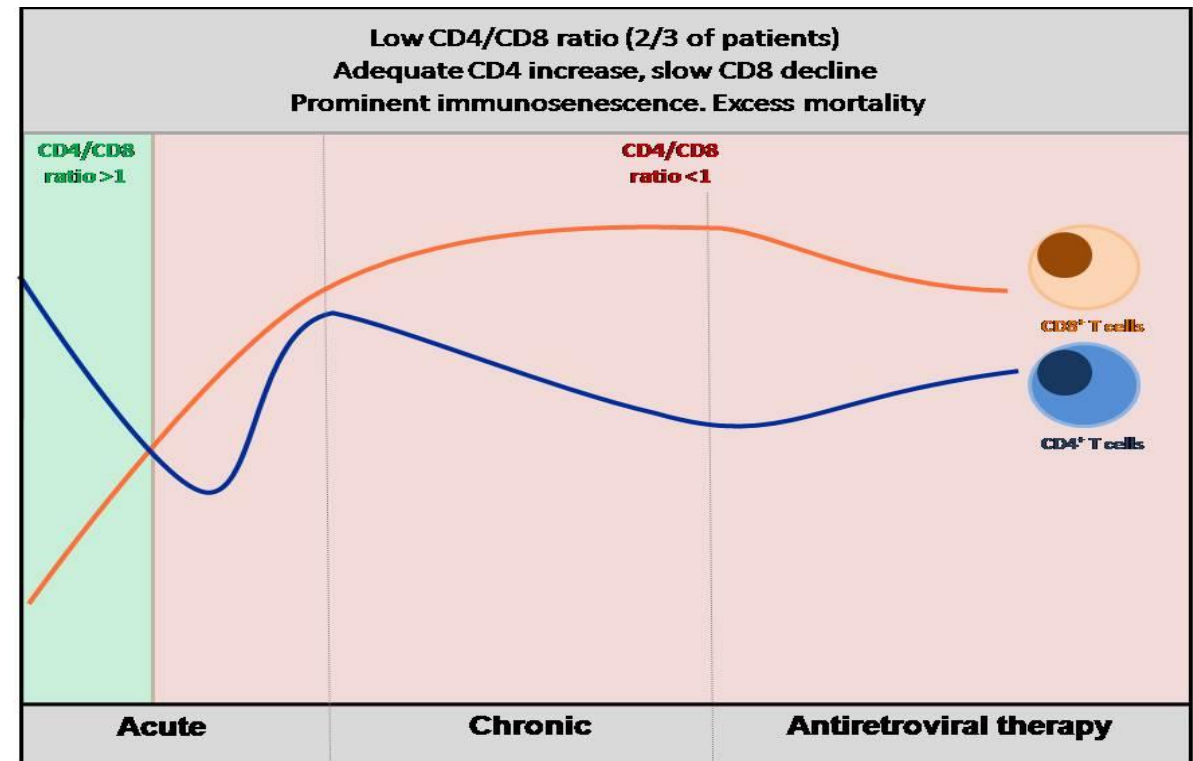
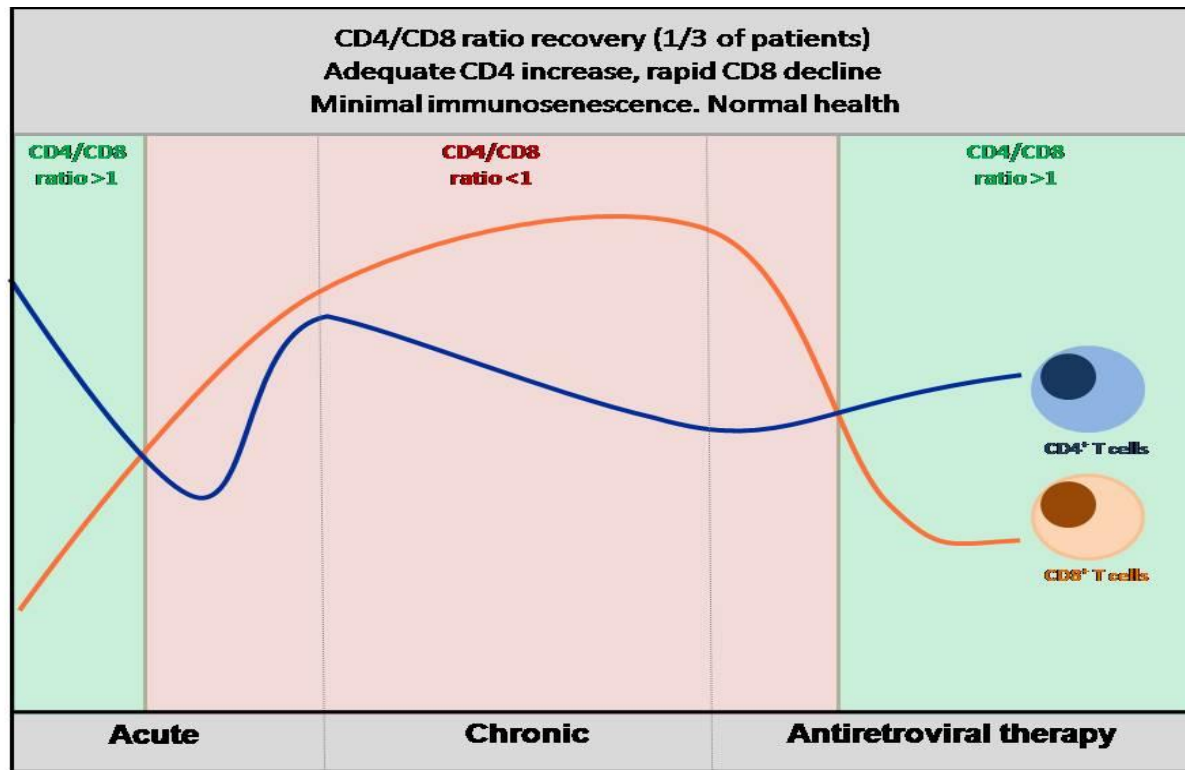


Neuhaus. JID 2010

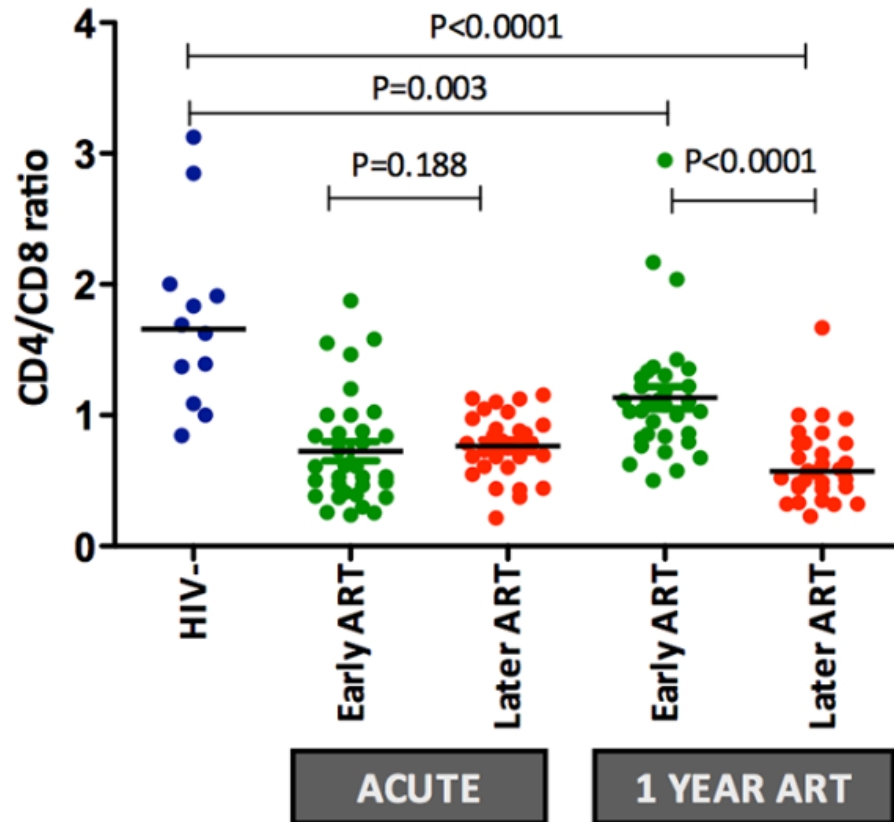


Grund et al. Plos One 2016 (see also: Duprez Plos One 2012)

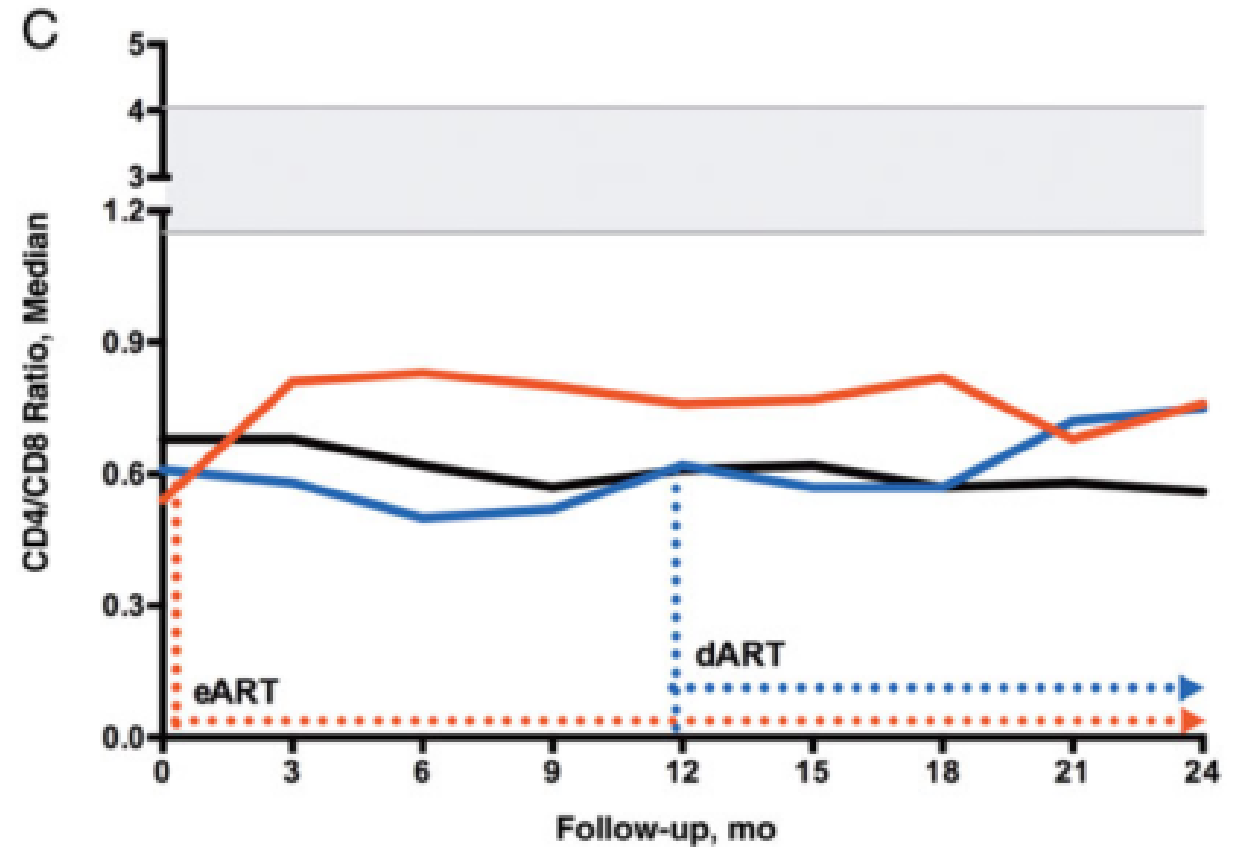
The CD4/CD8 ratio, a Proxy of Immunosenescence, Predicts Mortality During Treated HIV and is Impaired in 2/3 of Patients



Very Early ART Initiation Improves but do not Normalize Inflammatory Markers



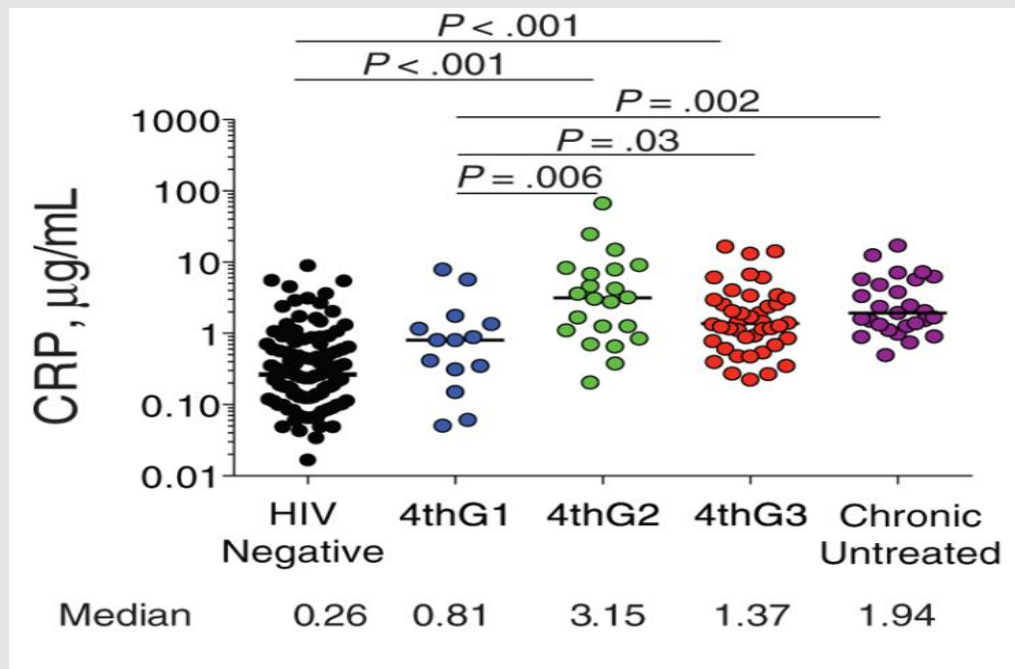
Serrano-Villar. Plos Pathogens 2014



Cao. CID 2016

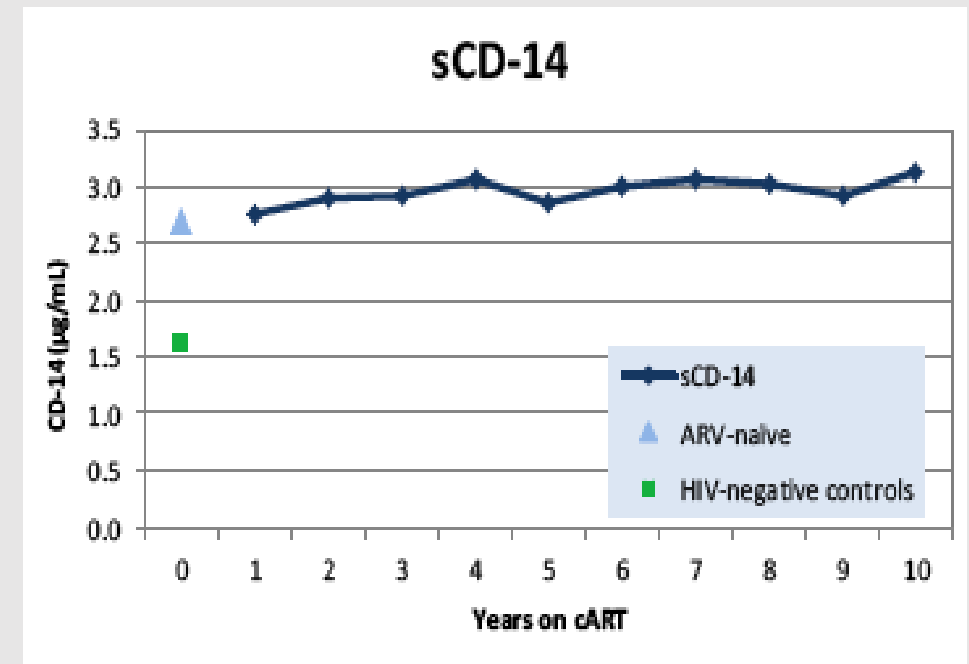
Very Early ART or Long-Term ART Improves but do not Normalize Inflammatory Markers

Inflammation Persists Despite Early Initiation of ART in Acute HIV Infection



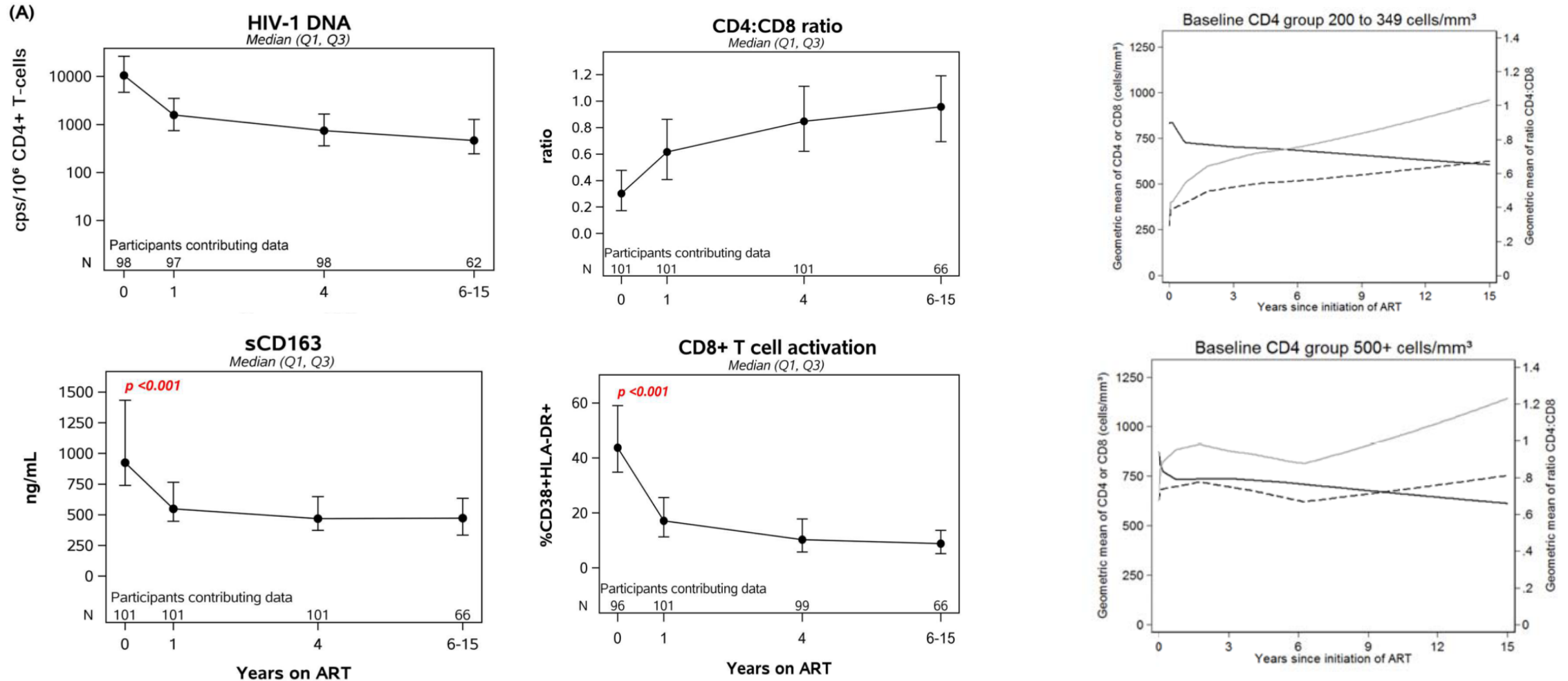
Sereti. CID 2017

Inflammatory Biomarkers Decline but Do Not Normalize after 10 Years of cART

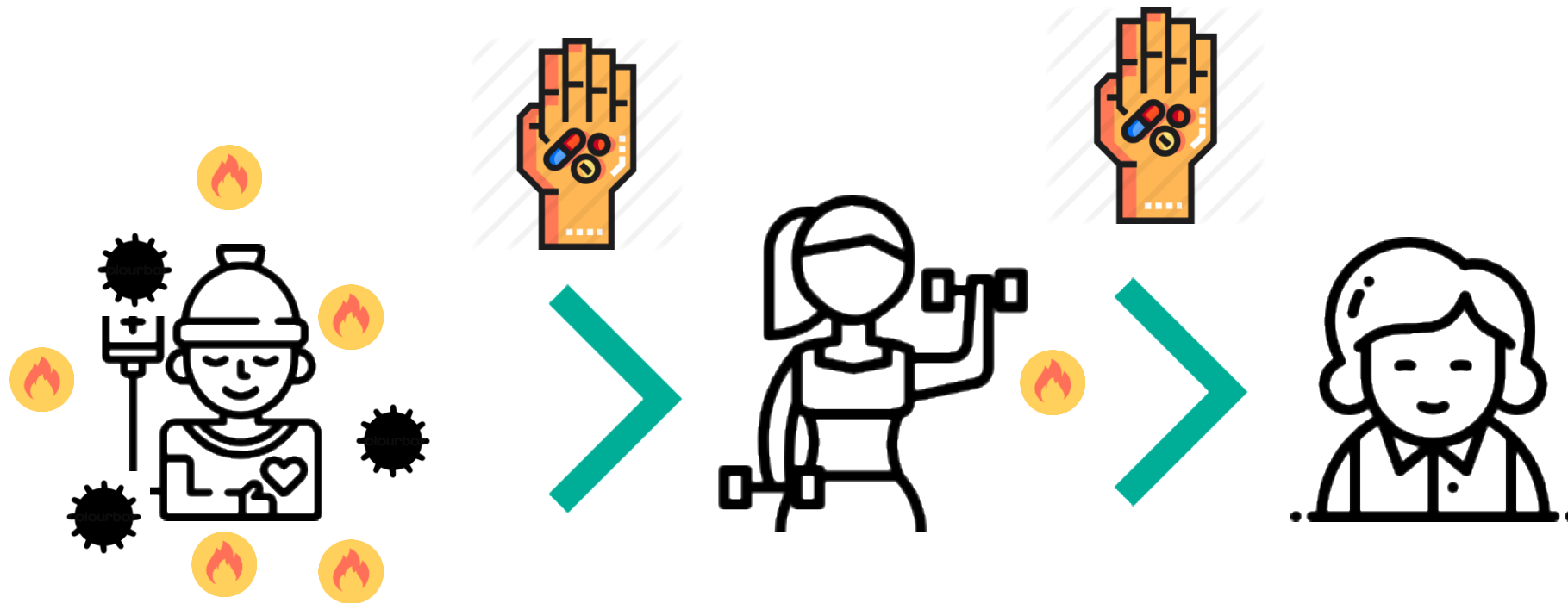


Lichtenstein. CROI 2015

But... Most Biomarkers Improve Slowly During Long-Term Triple ART, especially if ART is Initiated Early



Does ART fully restore health?



**What is the source
of inflammation?**

Immune Activation As a Tree

Leaves

End-organ diseases

Branches

IL-6 / Inflammation

D-dimer / Coagulation

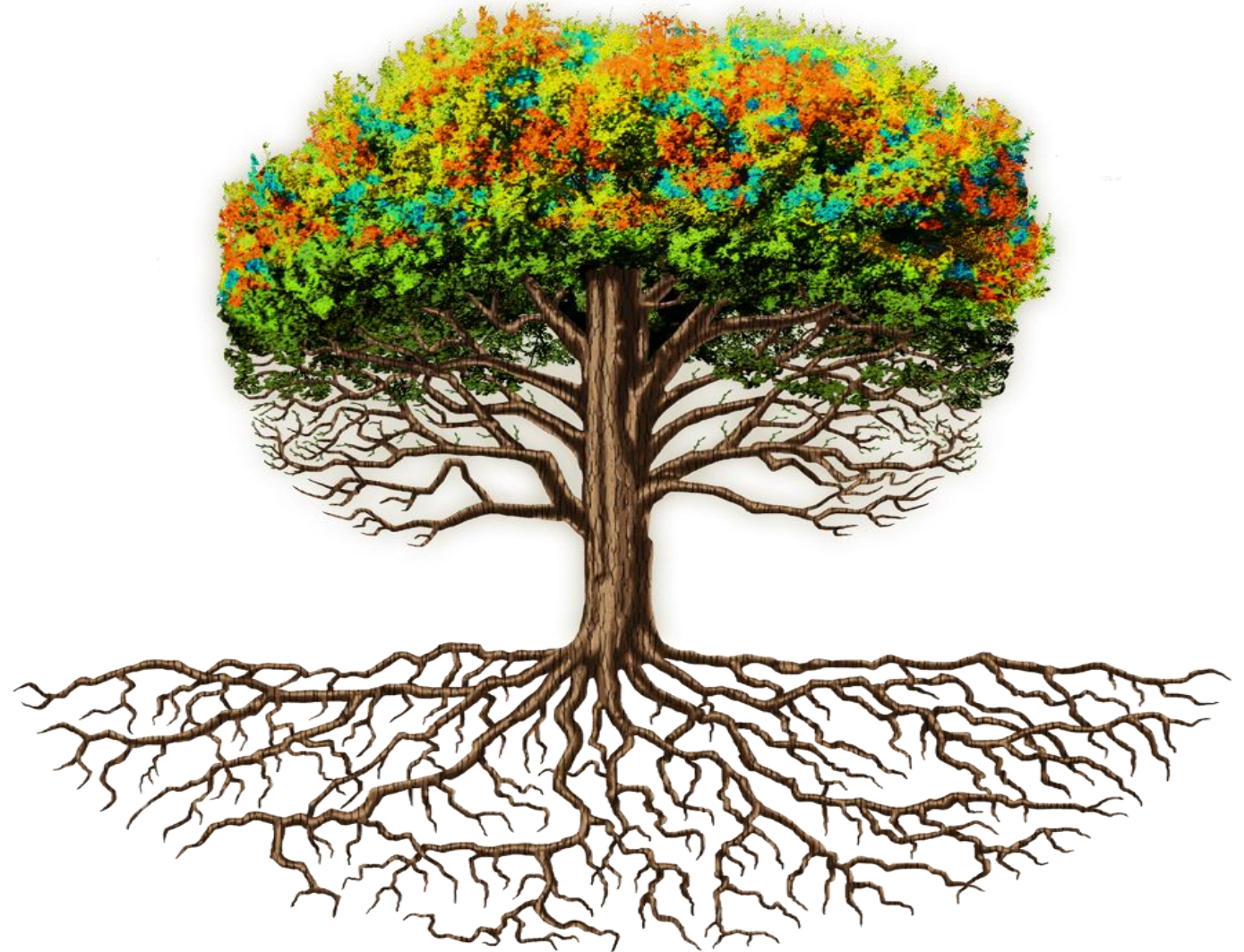
Lymphoid Fibrosis

Roots

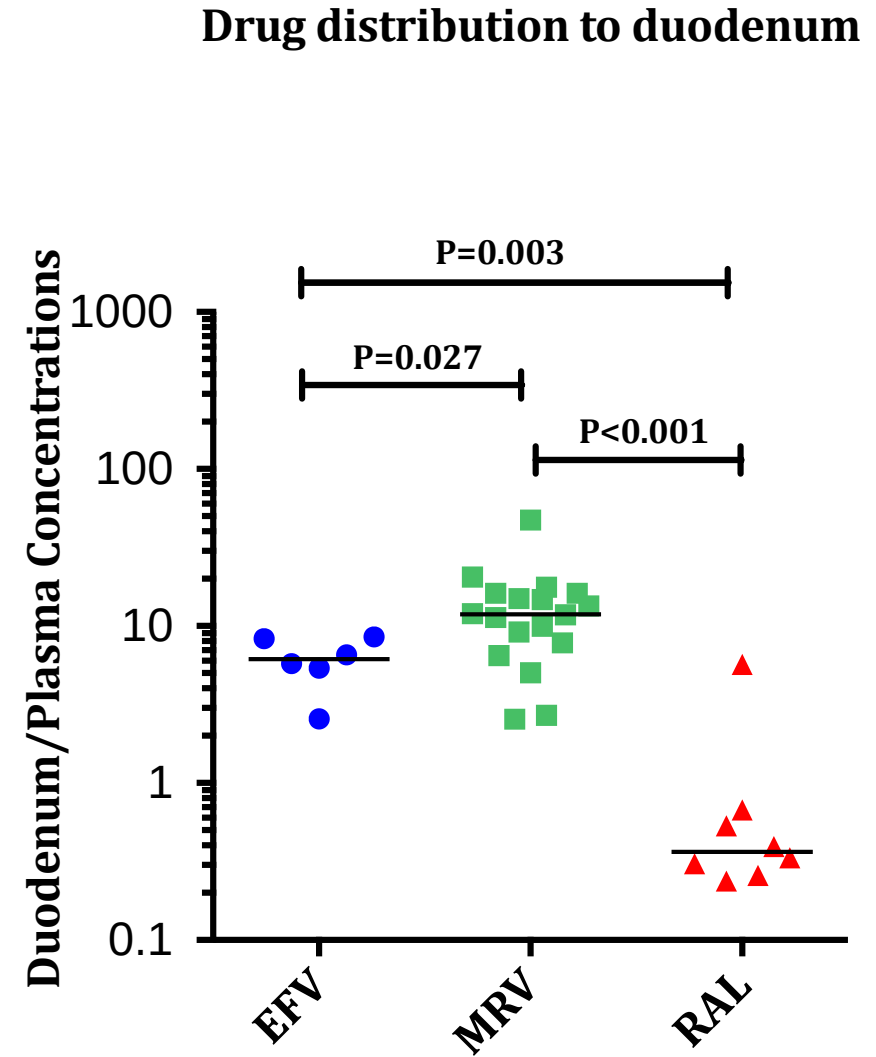
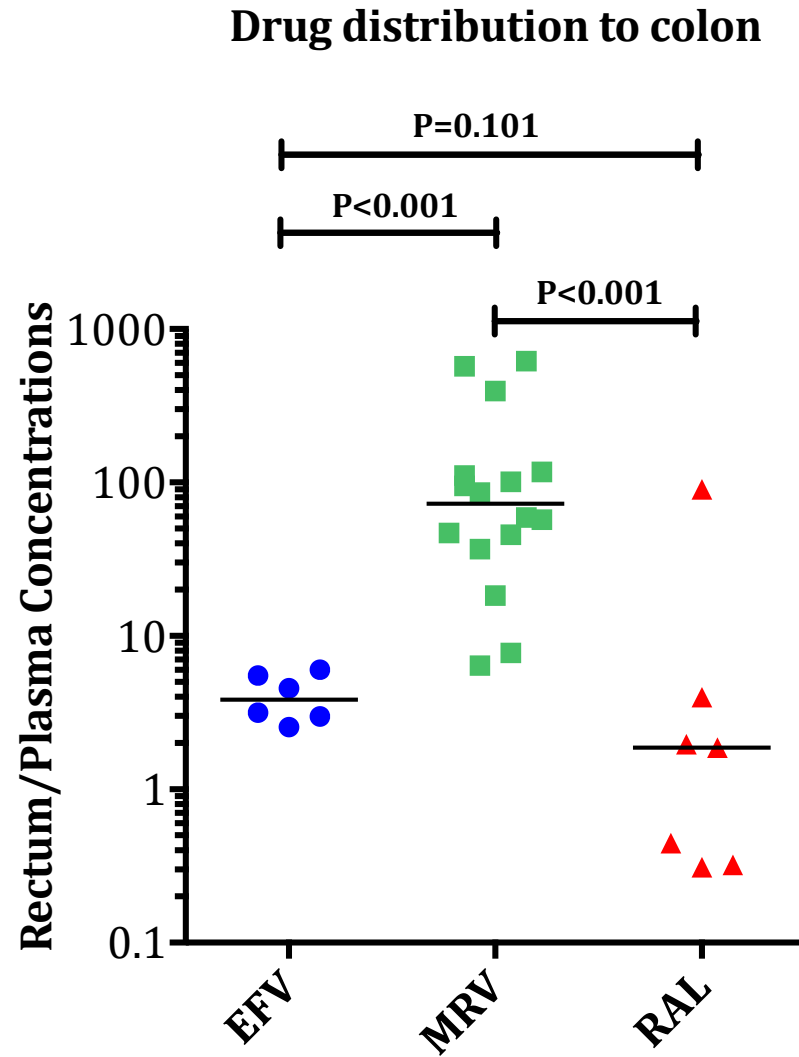
HIV reservoirs

CMV

Microbial translocation

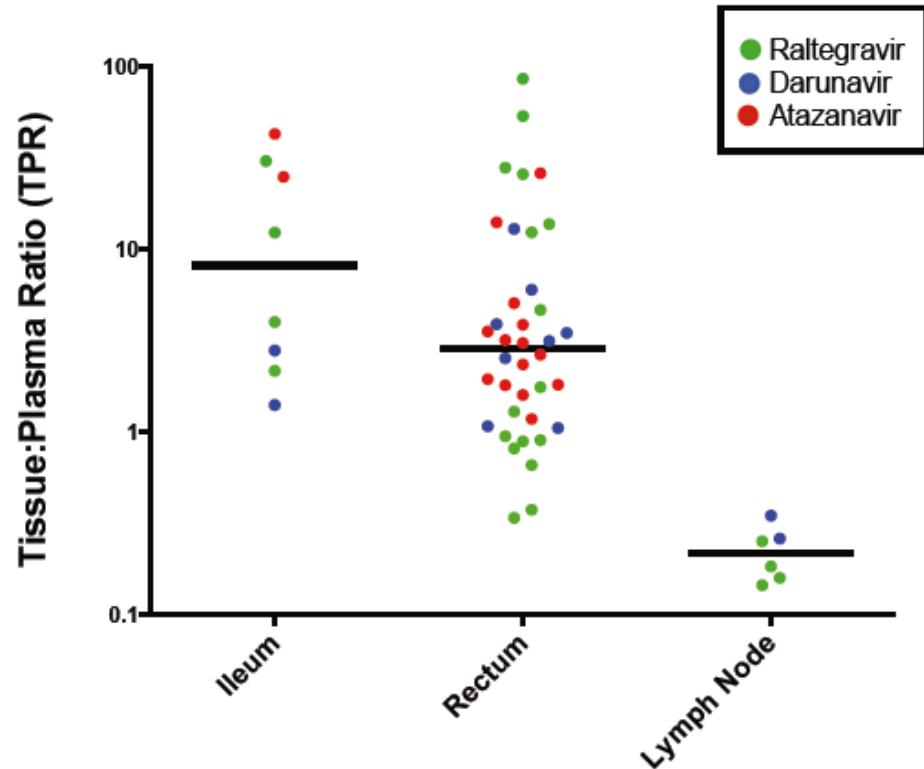


Variable penetration of ARV in tissue

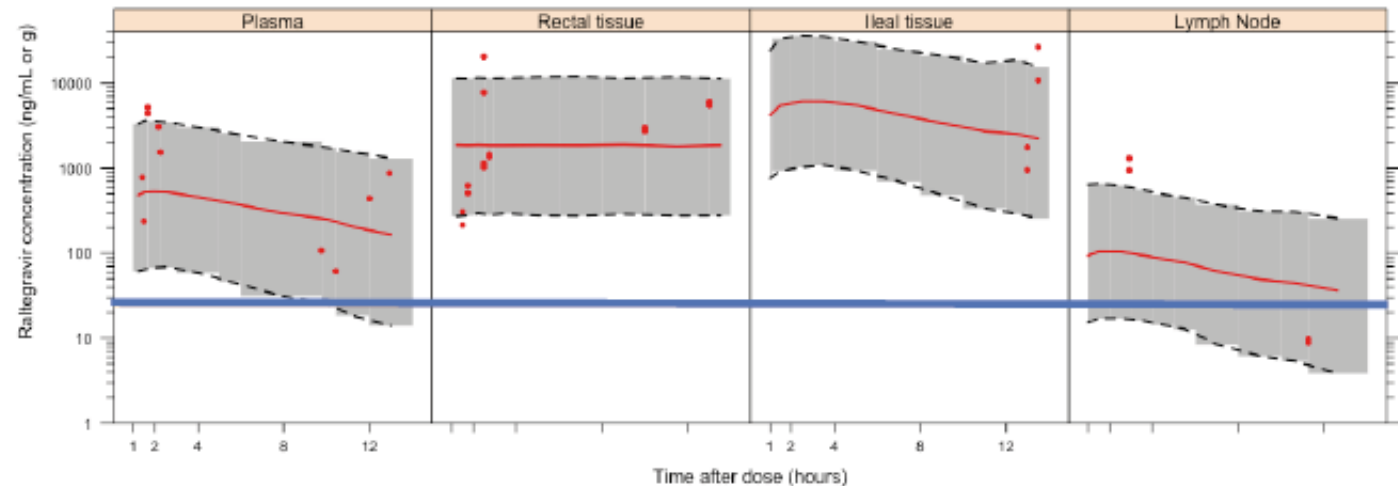


Limited Penetration of ARV in Lymph Nodes

Tissue:Plasma Ratios (TPRs) Higher in Ileum> Rectum>Lymph Node



RAL Predicted Lymph Node Tissue Concentrations Fall Below Target Concentrations to Suppress HIV



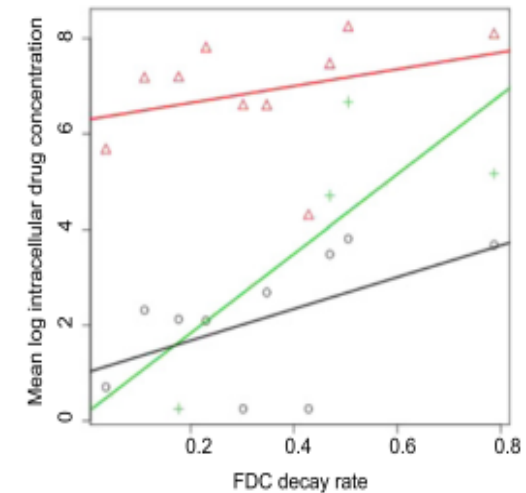
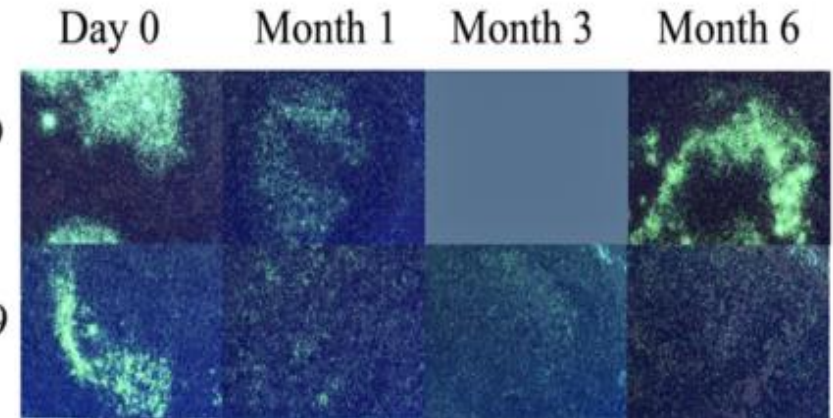
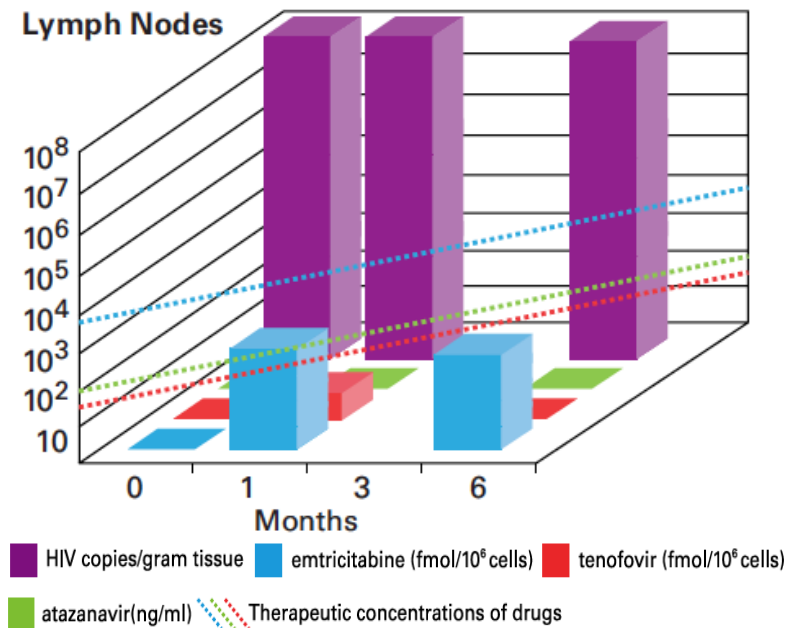
Simulated concentration time profiles with 95% confidence intervals (red curves) using observed data (red dots) and previously reported PK profile data for RAL (Savic Clin Pharmacol Ther. 2012) for Raltegravir. Blue line = concentration below which clinical virologic failure was observed in QDMRK study (Wenning 12th Intl. Workshop Clin. Pharmacol. HIV Ther., Miami, FL, 2011).

Variable penetration of ARV in tissue

PNAS

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

Courtney V. Fletcher^a, Kathryn Staskus^{b,1}, Stephen W. Wietgreffe^b, Meghan Rothenberger^c, Cavan Reilly^d, Jeffrey G. Chipman^e, Greg J. Beilman^e, Alexander Khoruts^c, Ann Thorkelson^c, Thomas E. Schmidt^c, Jodi Anderson^c, Katherine Perkey^b, Mario Stevenson^f, Alan S. Perelson^g, Daniel C. Douek^h, Ashley T. Haase^b, and Timothy W. Schacker^{c,2}



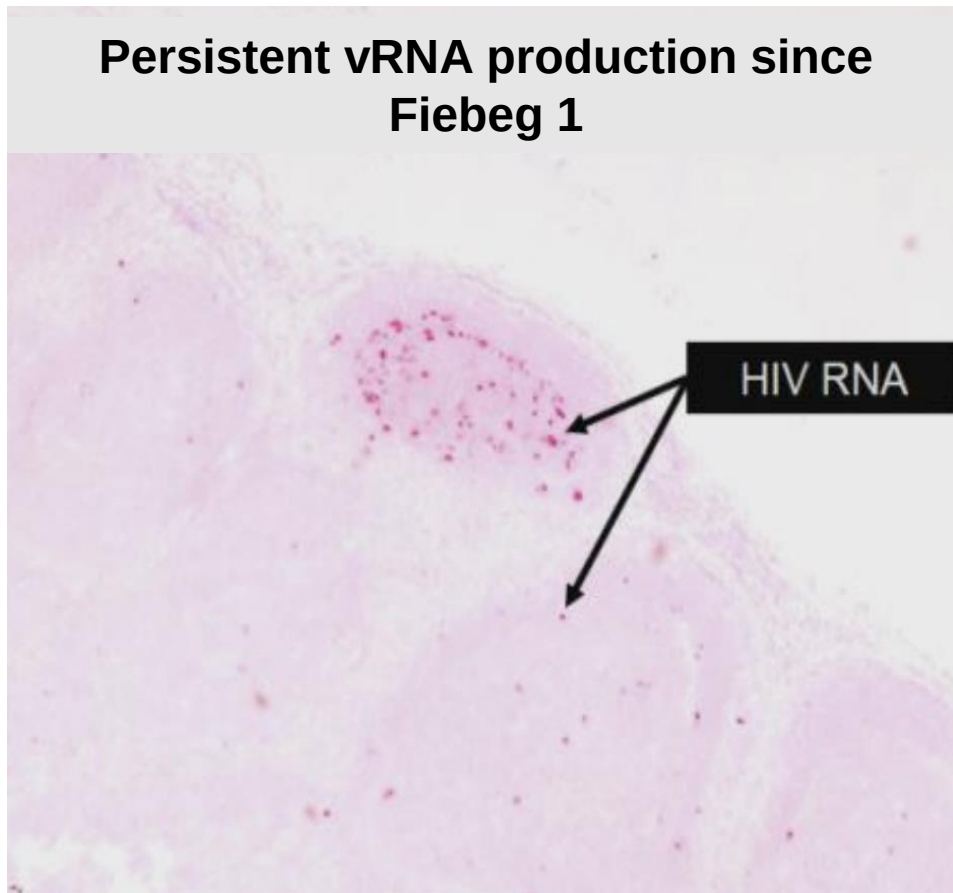
Fletcher, 19th CROI, Seattle 2012

Fletcher, PNAS 2014

(see also Lorenzo-Redondo, Nature 2016)

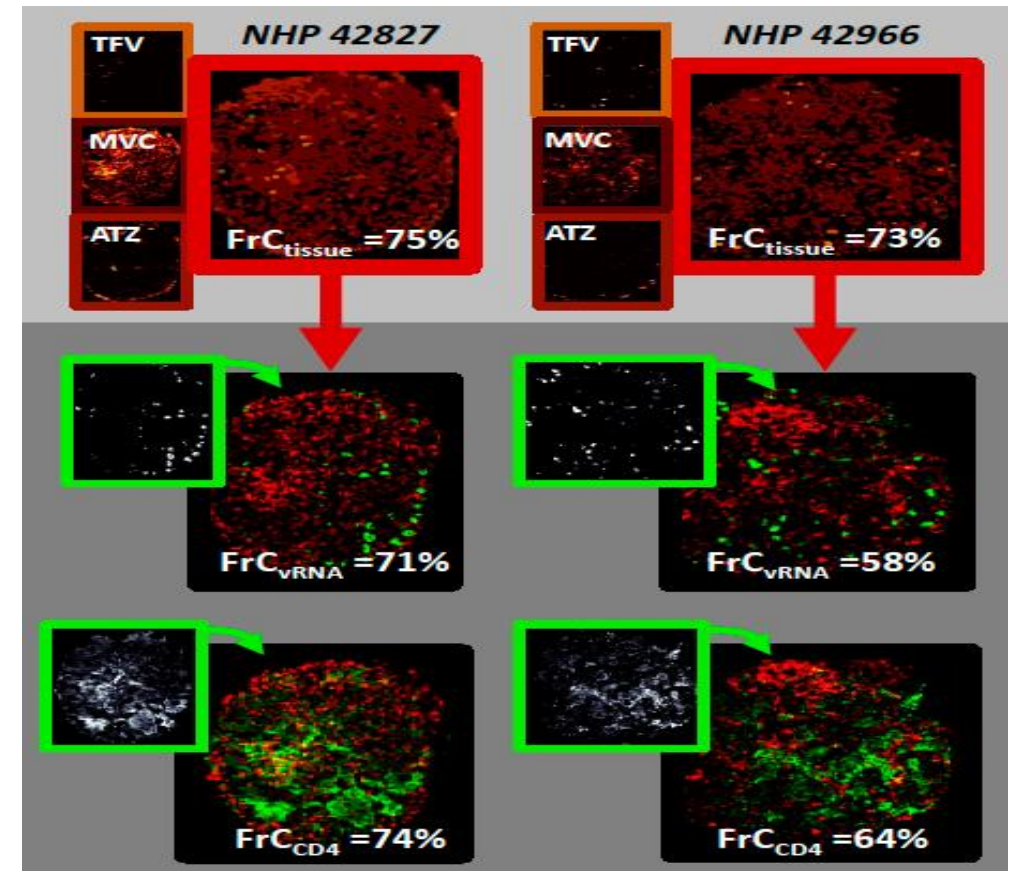
Ongoing viral replication and subtherapeutic ART concentrations in lymph nodes

Viral Production in Lymph Nodes Occurs Despite Very Early ART and is Linked with Lower Tissue Drug Distribution



Kroon. CROI 2018. Abstract #66

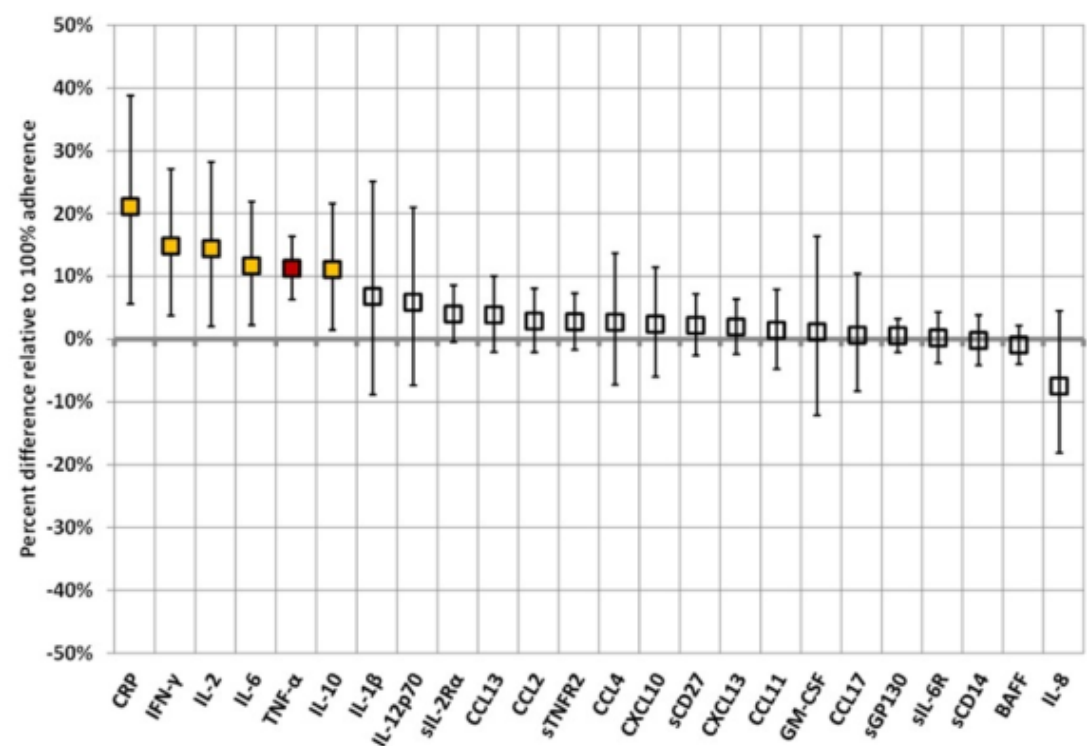
See also: #79 Bachman, Blips y HIV-DNA; #71 Rasmussen



Rosen. CROI 2018. Abstract#475

Suboptimal cART Adherence is Associated with Higher Levels of Inflammation Despite HIV Suppression

Porcentaje de diferencia en la concentración sérica de los biomarcadores (ajustado por edad, VHC, hipertensión, raza y tabaquismo).

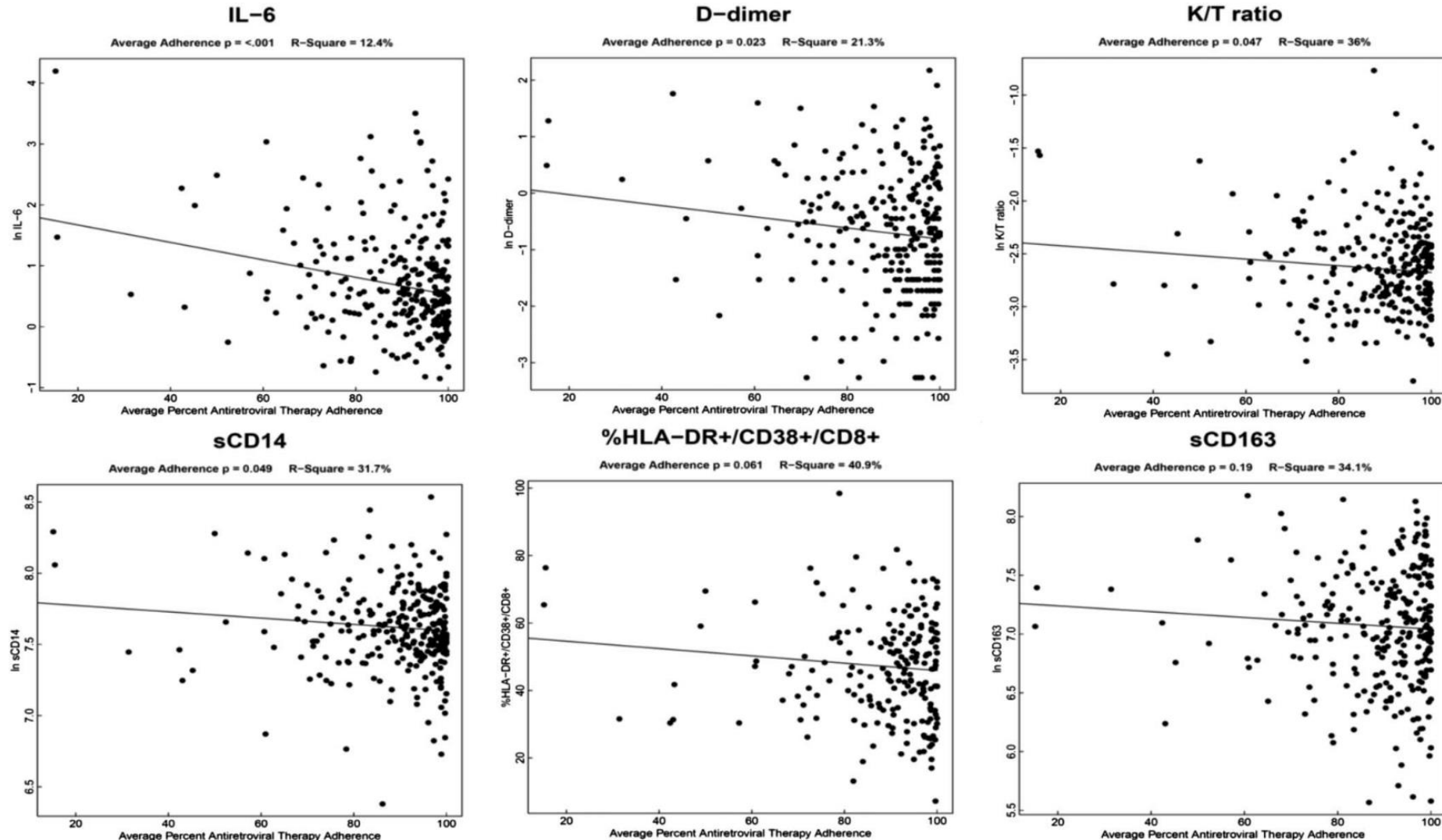


	<100% vs 100% (6-m)	
	Estimado	p
TNF-α	11,2%	<0,001
IFN-γ	14,8%	0,008
CRP	21,1%	0,006
IL-2	14,4%	0,022
IL-10	11,1%	0,023
IL-6	11,6%	0,014

Abreviaturas: BAFF, factor activador de las células B; CCL, quimioquinas C-C ligando; CXCL quimioquinas CXC ligando; GM-CSF, factor estimulante de granulocitos y macrófagos ; IFN-γ, interferón gamma; IL, interleucina; sCD14, CD14 soluble; sCD27, CD27 soluble; sgp130, glicoproteína soluble 130; sIL-2Rα, receptor soluble IL-2; sIL-6R, receptor soluble IL-6; sTNF-R2, receptor soluble del factor de necrosis tumoral; TNF-α, factor de necrosis tumoral α; CRP, proteína C reactiva.

Abreviaturas: IFN-γ, interferón gamma; IL, interleucina; TNF-α, factor de necrosis tumoral α; CRP, proteína C reactiva.

Suboptimal cART Adherence is Associated with Higher Levels of Inflammation Despite HIV Suppression



Suboptimal cART Adherence is Associated with Higher Levels of Inflammation Despite HIV Suppression

TABLE 2. Antiretroviral Adherence and Biomarkers of Inflammation, Coagulopathy, and CD8⁺ T-Cell Activation 6 Months After Treatment Initiation in Study Participants Who Achieved an HIV VL of <400 Copies Per Milliliter and <40 Copies Per Milliliter

Biomarker	Full Model For <400 copies/mL*				Full Model For <40 copies/mL*			
	No. Participants	Percent Reduction For Each 10% Increase in Adherence†	95% CI	P	No. Participants	Percent Reduction For Each 10% Increase in Adherence†	95% CI	P
IL-6	247	−14.7	−21.0 to −7.9	<0.0001	121	−11.3	−20.9 to −0.6	0.040
D-dimer	251	−10.5	−18.3 to −2.0	0.017	125	−11.0	−21.5 to 1.0	0.070
K/T ratio	250	−3.0	−6.0 to 0.3	0.070	122	−2.6	−6.9 to 1.9	0.247
sCD14	251	−2.7	−5.0 to −0.3	0.028	124	−1.5	−4.6 to 1.9	0.382
% HLA-DR ⁺ /CD38 ⁺ CD8 ⁺ ‡	184	−1.2	−2.5 to 0.03	0.056	92	−1.1	−3.1 to 0.9	0.272
sCD163	251	−3.1	−6.8 to 0.8	0.119	124	−7.4	−12.4 to −2.0	0.009

*Adjusted for baseline biomarkers, age, gender, and baseline values of CD4⁺ T-cell count, HIV VL, depression (yes/no), and alcoholism (yes/no).

†Percent change from baseline after 6 months of therapy.

‡Absolute decrease in proportion of CD8⁺ T cells that coexpress HLA-DR⁺/CD38⁺ (not percent decrease).

K/T, Kynurenine/tryptophan; sCD14, soluble CD14; sCD163, soluble CD163.

**Is there a role of ART families
on inflammation?**

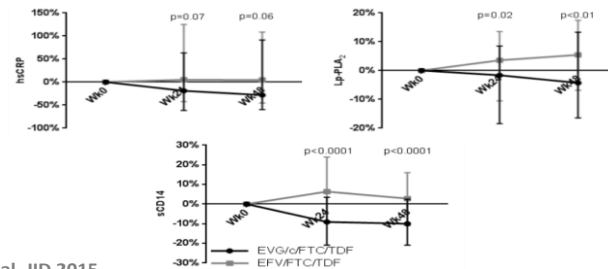
To be Defined: Likely Stronger Effects of INSTI-based First-Line ART

Effects of First-Line EFV vs. EVGc in Monocyte Activation and Vascular Inflammation

Larger decreases of sCD14, hs-CRP and Lp-PLA2 with EVGc

300 ART-naïve patients
Double-blind, randomized, single center study
FTC/TDF + EFV VS. EVGc

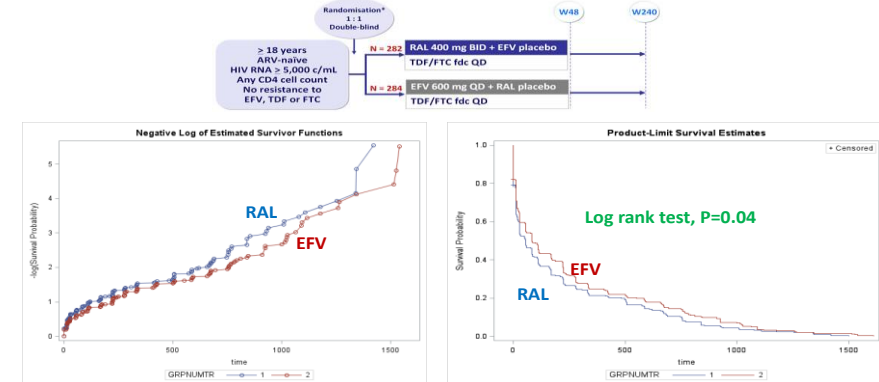
Monocyte activation (sCD14, sCD163), systemic (sTNF-RI, IL-6, hsCRP) and vascular inflammation (Lp-PLA2)



Hileman et al. JID 2015

Hileman. JID 2015

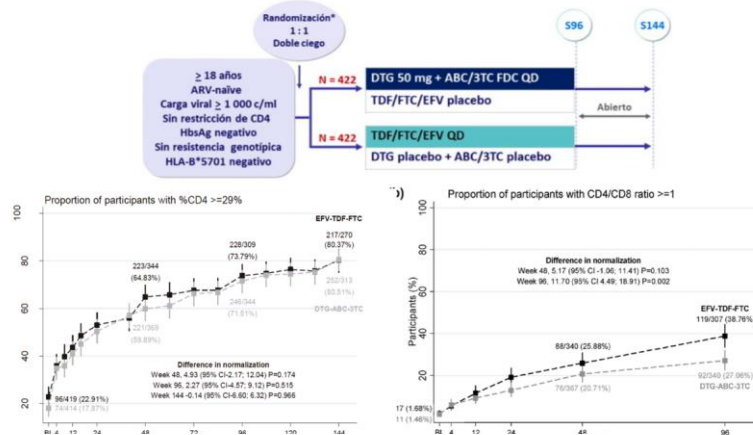
Raltegravir Normalized the CD4/CD8 Ratio Faster than Efavirenz in STARTMRK trial



Serrano-Villar, JAC 2016. (see also: Salvador-Guillouet, Plos One 2015)

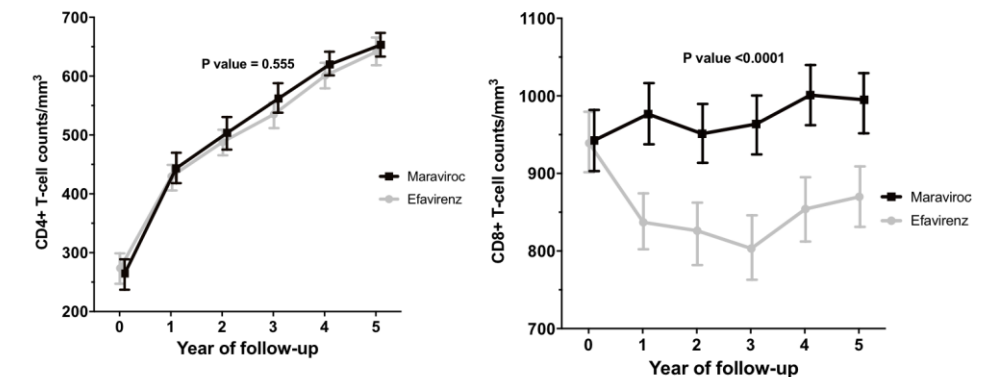
Serrano-Villar. JAC 2016

SINGLE: Effects of DTG+ABC/3TC vs. EFV/TDF/FTC on the CD4/CD8 ratio in treatment-naïve HIV-infected individuals



Blanco. Clin Mic Infec 2017

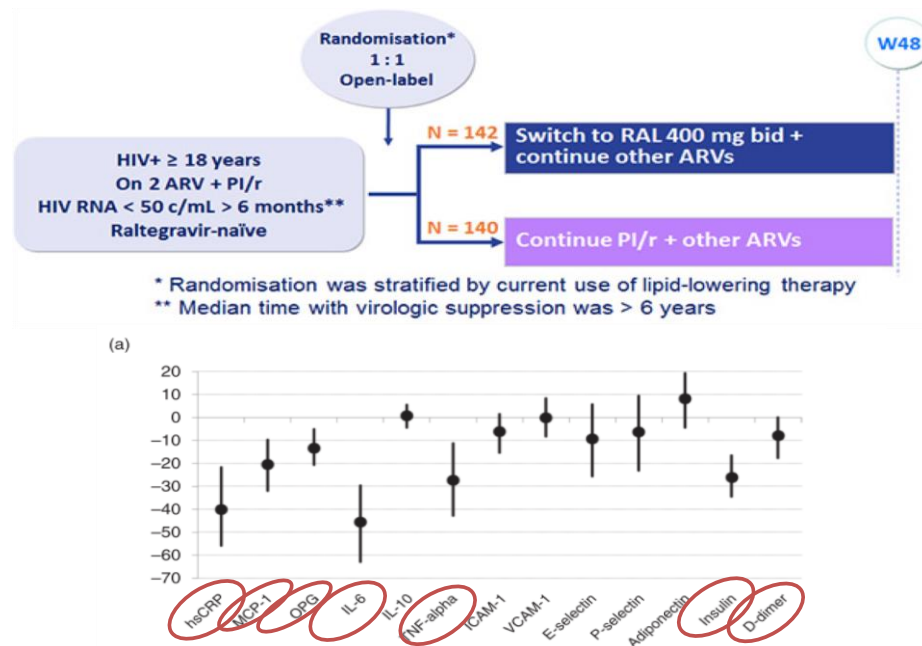
The effects of maraviroc versus efavirenz in combination with zidovudine/lamivudine on the CD4/CD8 ratio in treatment-naïve HIV-infected individuals



Serrano-Villar. Antimicrob Agent Chemother 2017

... and in Switching

Impact of switching from PI to raltegravir on cardiovascular biomarkers

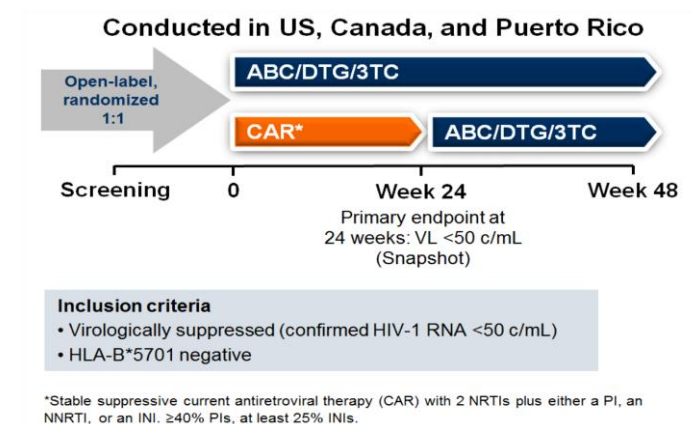


Martínez. AIDS 2012

Inflammatory markers improved after switching to raltegravir

Martínez. AIDS 2012

Effects on Inflammation of Switch to ABC/3TC/DTG in STRIVING



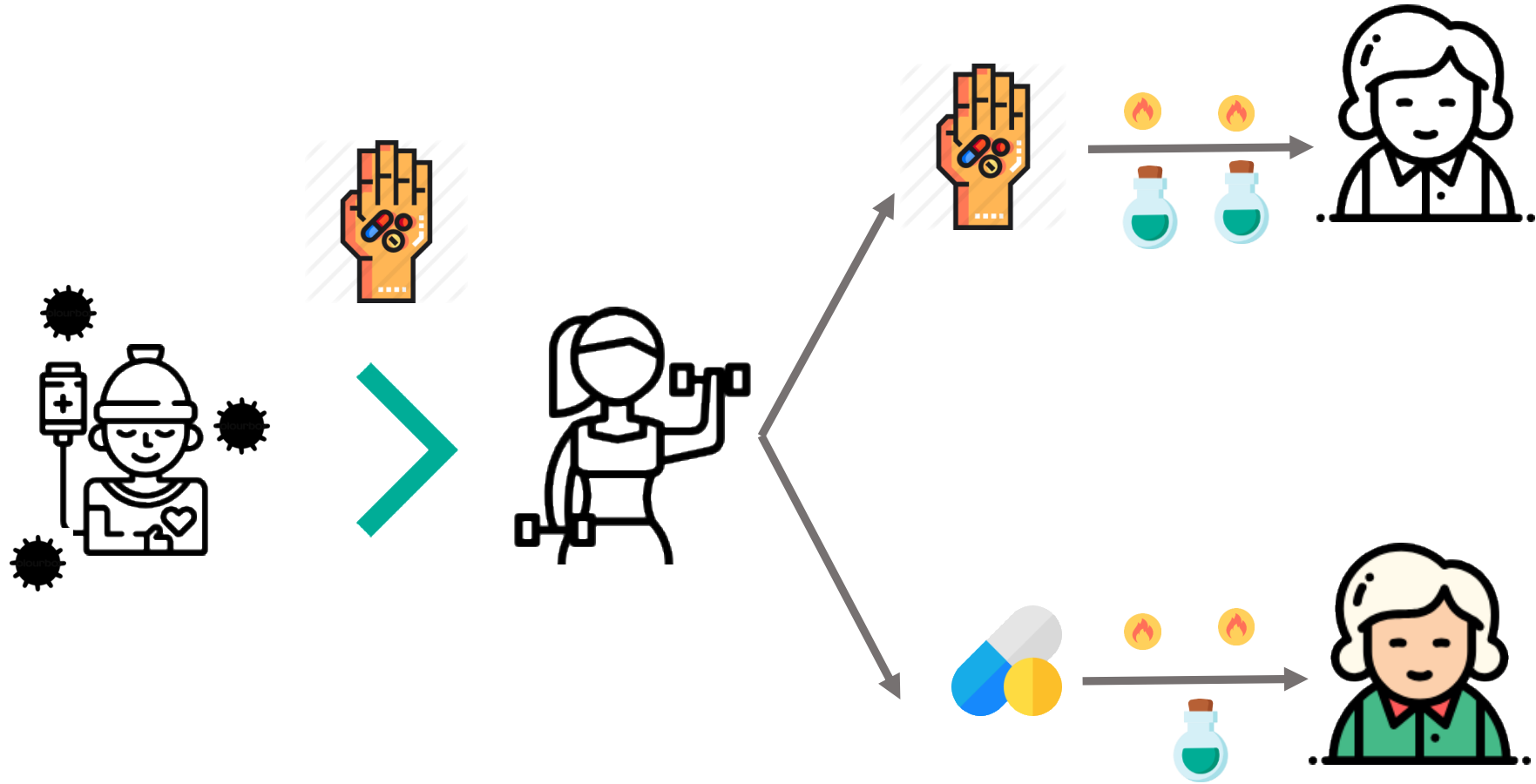
C-reactive protein (hs-CRP), interleukin-6 (IL-6), D-dimer, soluble vascular cell adhesion molecule (sVCAM), soluble CD14 and CD163 (sCD14, sCD163), and intestinal fatty acid-binding protein (I-FABP) levels were measured as secondary endpoints

Inflammatory markers improved after switching to ABC/3TC/DTG

Lake. CROI 2016

**What do we know and what
we don't know about the
consequences of the number
of antiretrovirals?**

Rationale for Dual Therapy



Essay

The Ethics of Switch/Simplify in Antiretroviral Trials: Non-Inferior or Just Inferior?

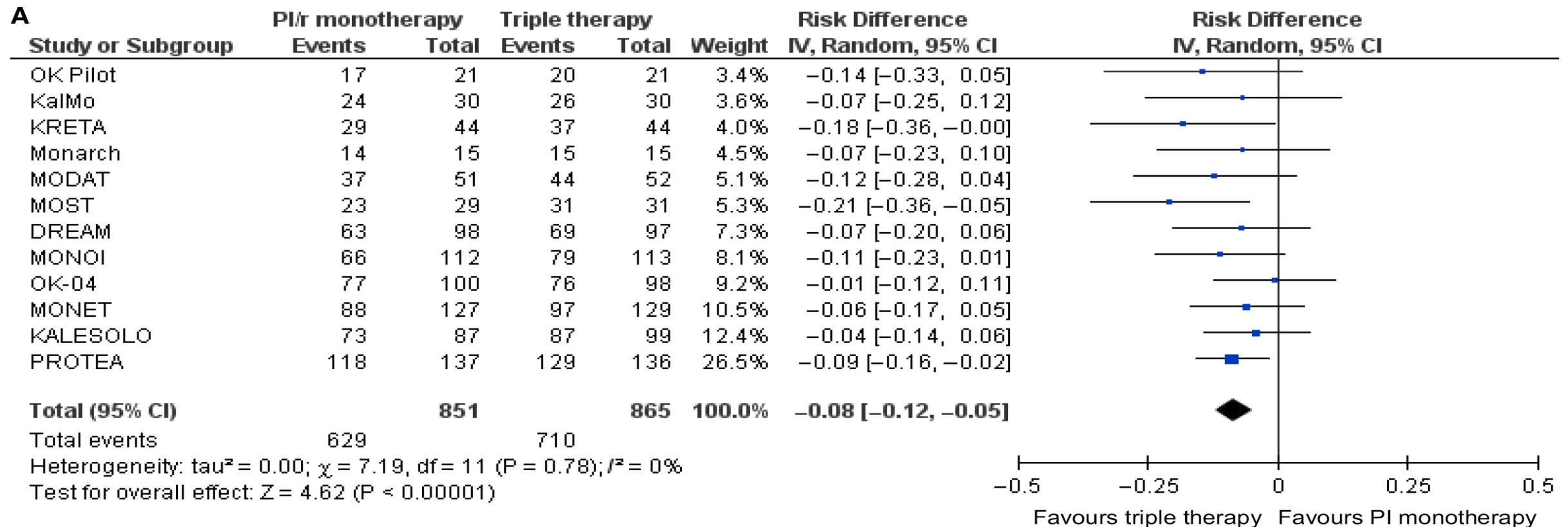
Andrew Carr^{1,2*}, Jennifer Hoy^{3,4}, Anton Pozniak⁵

Summary Points

- The high efficacy of antiretroviral therapy has resulted in more trials that switch or simplify existing therapy in patients whose HIV is fully controlled.
- The primary outcome of about half of these trials is virological non-inferiority. As participants already have fully controlled HIV on existing therapy, these trials offer no virological benefit.
- Many trials (i) enrol patients who cannot benefit with the switch, (ii) do not capture (or report) all potential risks, and (iii) are designed with a view to a pharmaceutical company's profits rather than participant benefit.
- A switch/simplification trial is only ethical if participants can meaningfully benefit from the treatment change and are more likely to benefit than suffer harm, and if the study is powered to assess the key expected benefit and reports all end points.

MONOTHERAPY META-ANALYSIS

Switch equals failure

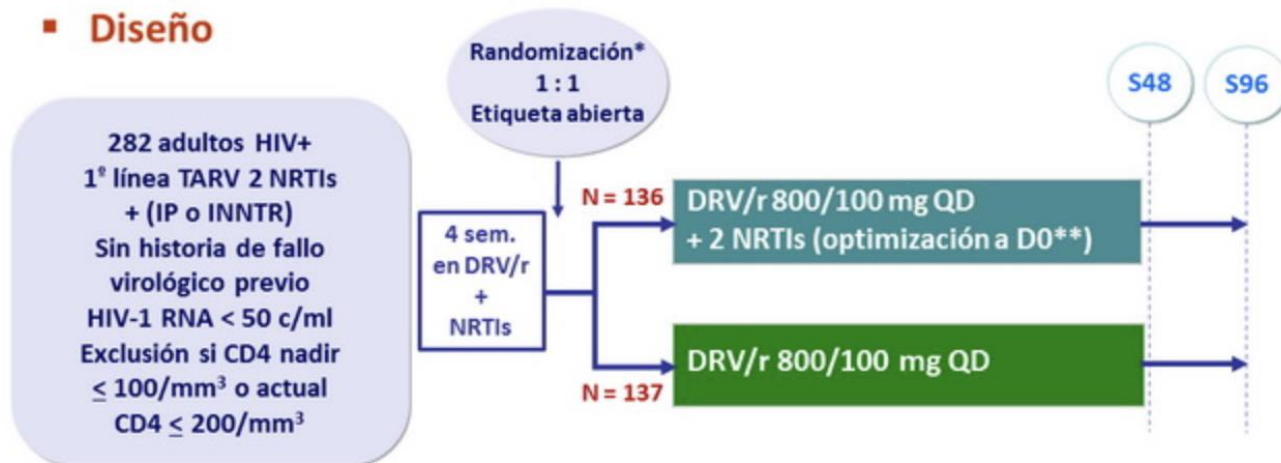


“PI/r monotherapy showed a higher risk of plasma HIV-1 RNA elevations”

PROTEA Study

HIV-1 RNA in CSF samples at Week 48

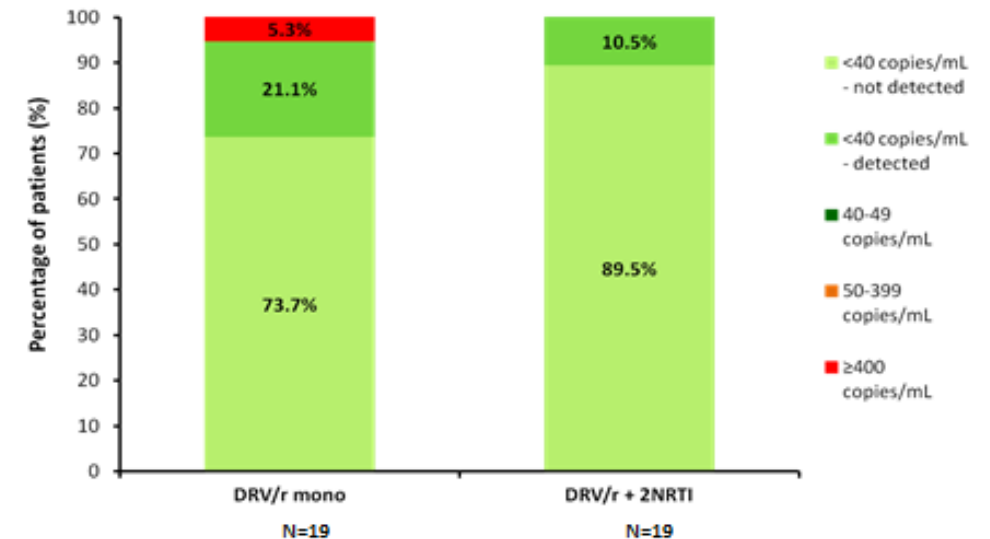
■ Diseño



* La randomización fue estratificada por status anti-HCV (+ o -)

** TDF, ABC o ZDV + 3TC o FTC

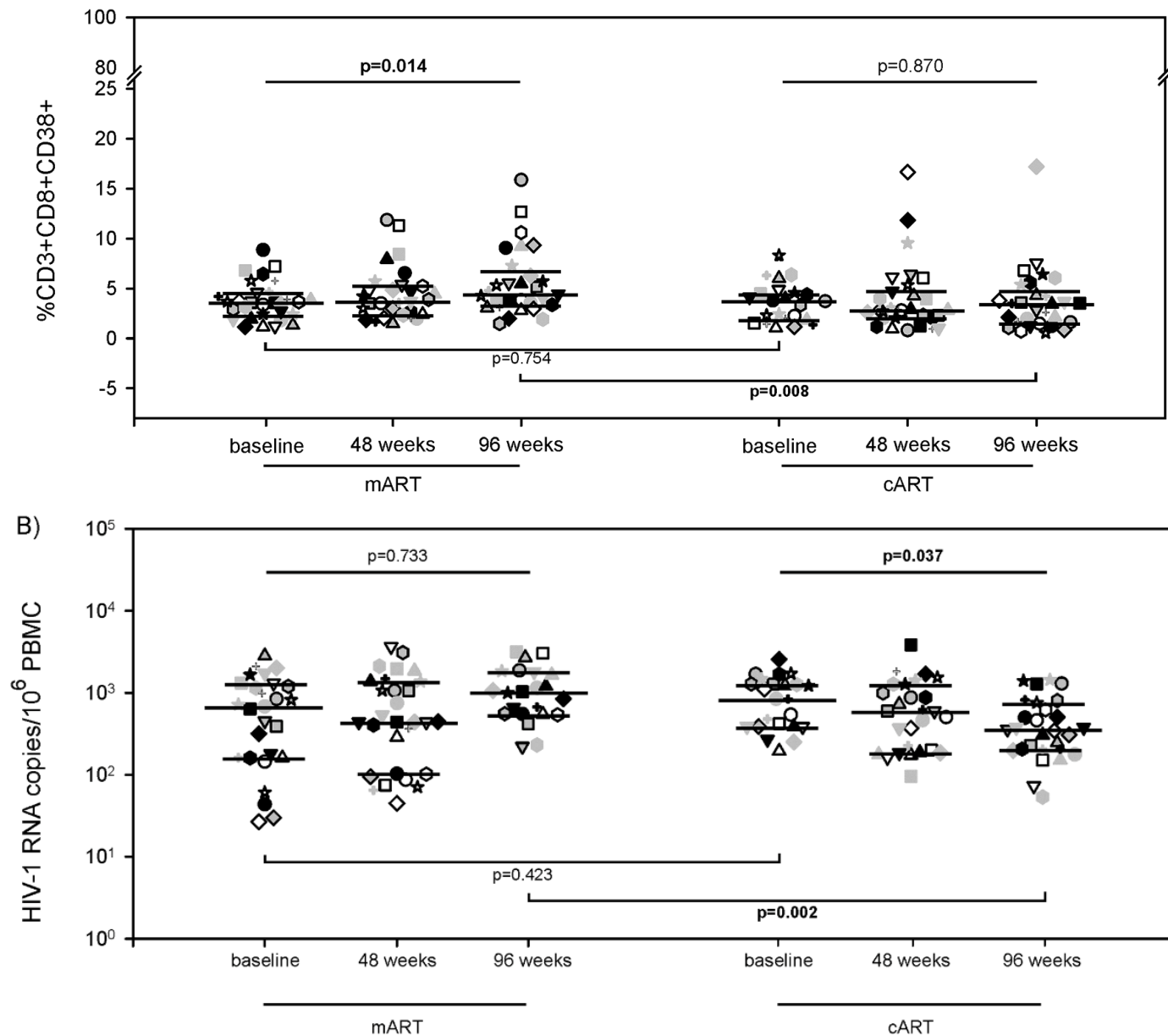
HIV-1 RNA in CSF samples at Week 48 for patients undetectable at baseline (<40 copies/mL – not detected)



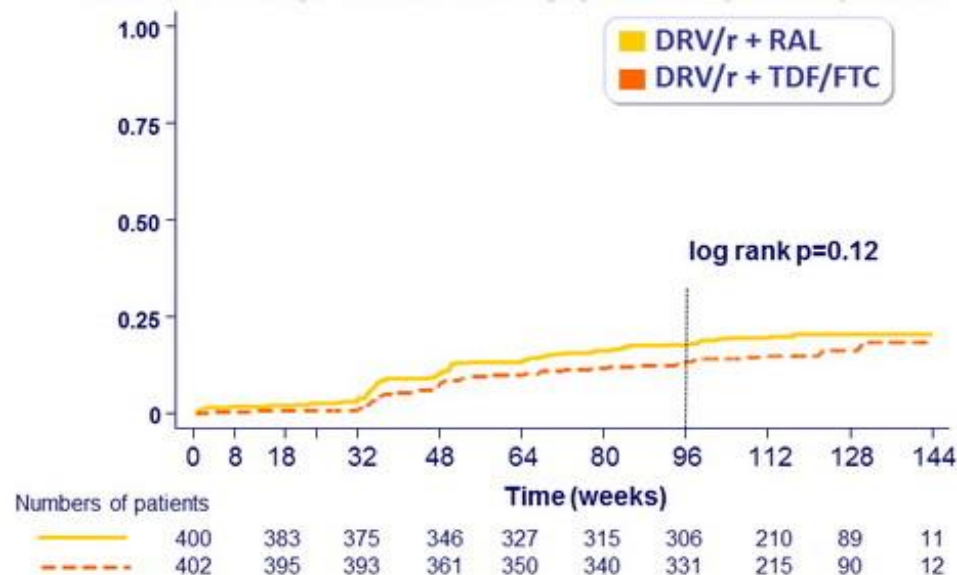
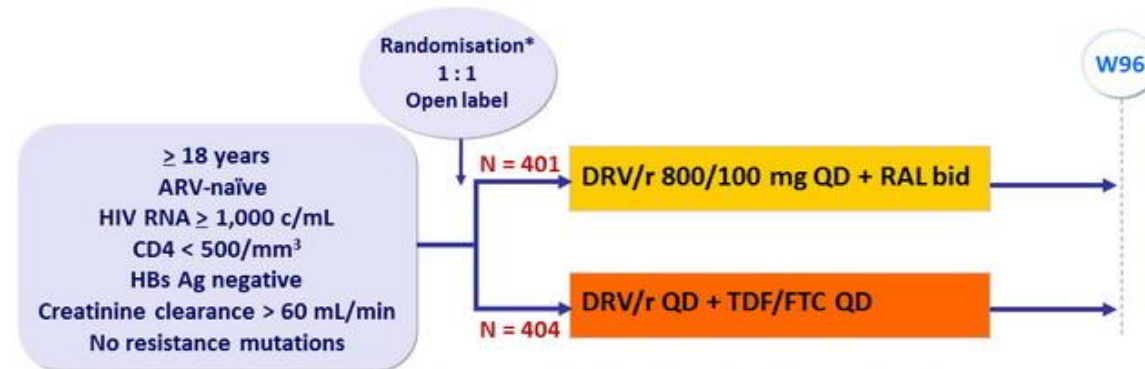
There were 2 patients with HIV-1 RNA <40 copies/mL (target detected) at baseline in the CSF. Both patients had HIV RNA <40 copies/mL (target not detected) at Week 48.

- Dos pacientes en la rama monoterapia con CD4 nadir < 200/mm³ desarrollaron viremia tanto en LCR como en plasma, con un caso sintomático.

Immune Activation in mART-treated and cART-treated patients



NEAT 001/ANRS 143: DRV/r+RAL vs DRV/r+TDF/FTC



- DRV/ r + RAL was non inferior to DRV/ r + TDF/FTC for the composite primary endpoint based on clinical and virological failure
- The NtRTI -sparing strategy was less efficacious than the standard regimen in patients with CD4 cell count <200/mm³ at treatment start.
- Despite a low rate of virological failure in both arms, emergence of resistance mutations was higher in the raltegravir group.