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

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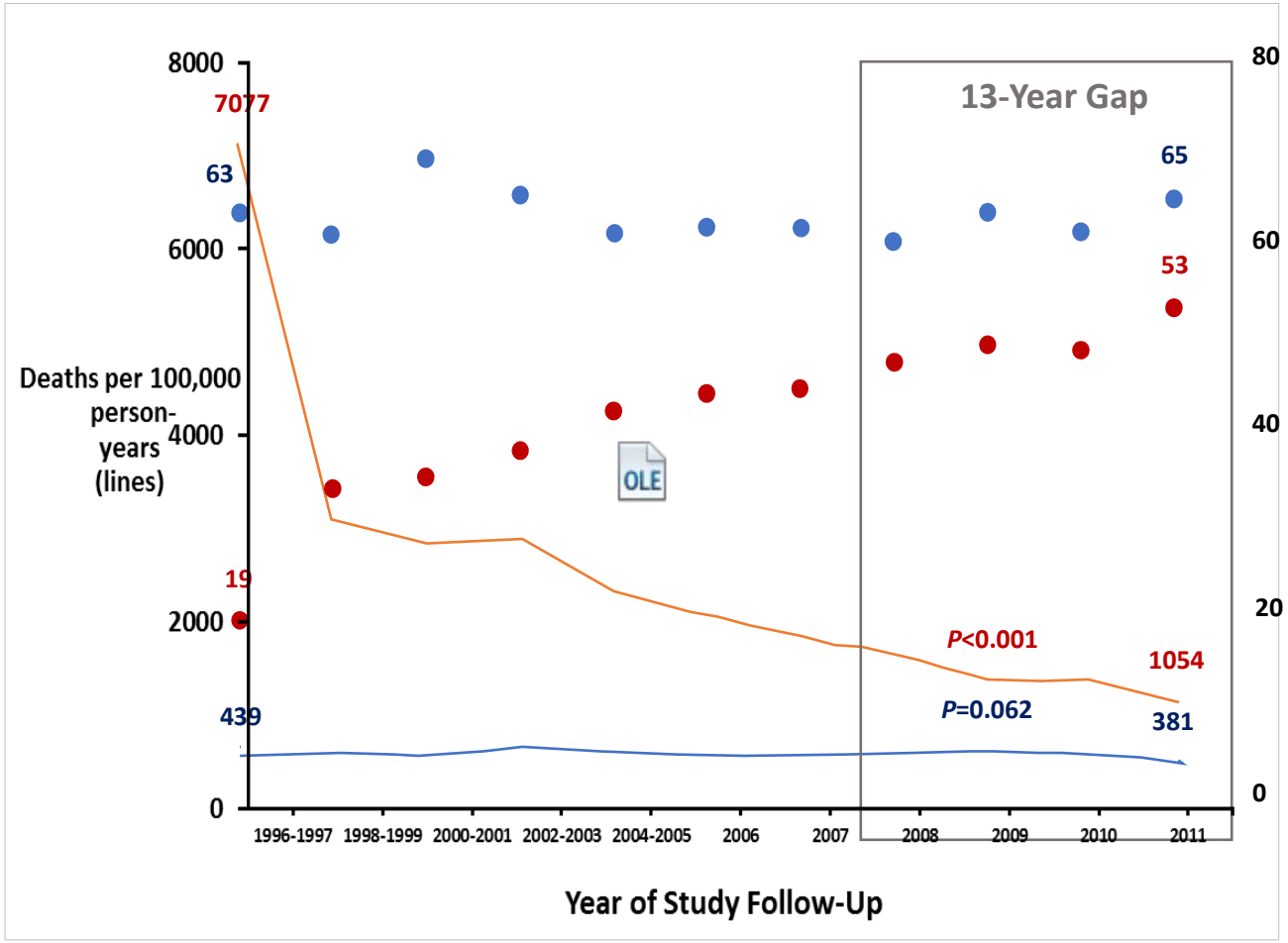
Disclosures

El Dr. Sergio Serrano ha prescrito:

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

What is the main unmet goal of ART?

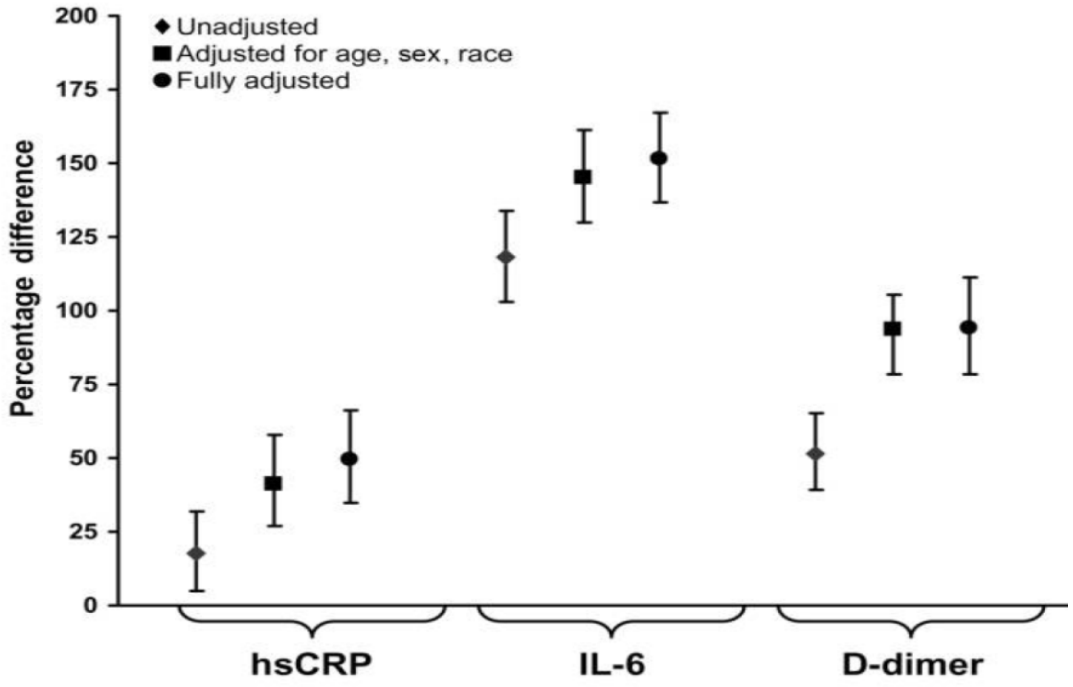
Kaiser Permanente HIV Cohort: Narrowing the Gap in Life Expectancy for HIV+ vs HIV-Individuals



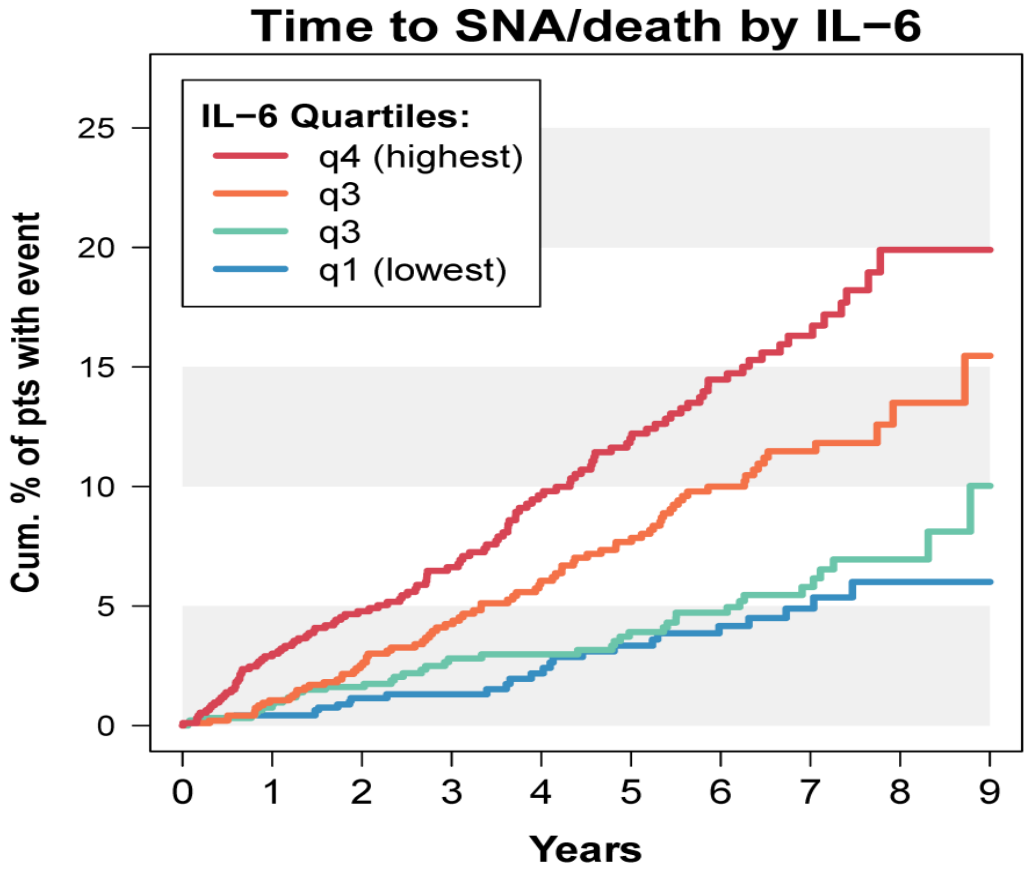
8 year gap with ART initiation at CD4 ≥ 500. Life expectancy ↓ Blacks & IVDU. ↓ Hispanics
Gap narrowed if no hepatitis, drug/alcohol, or smoking

Marcus J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 54.

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

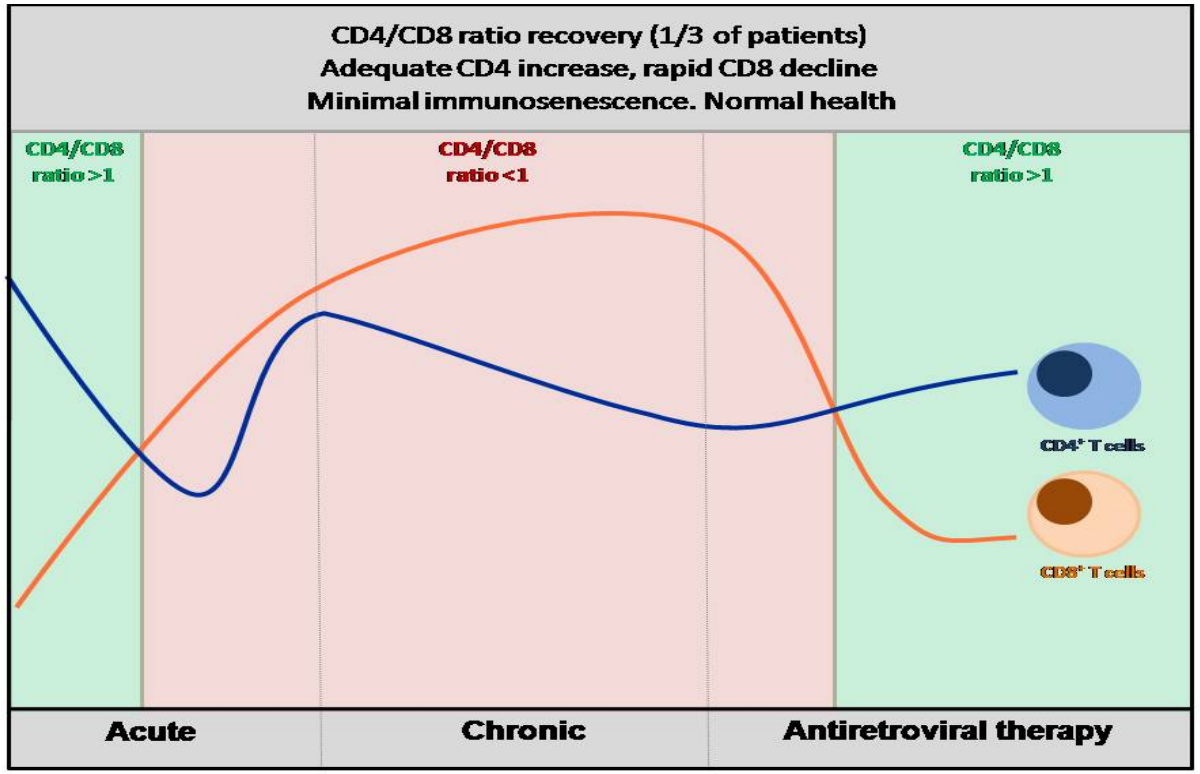


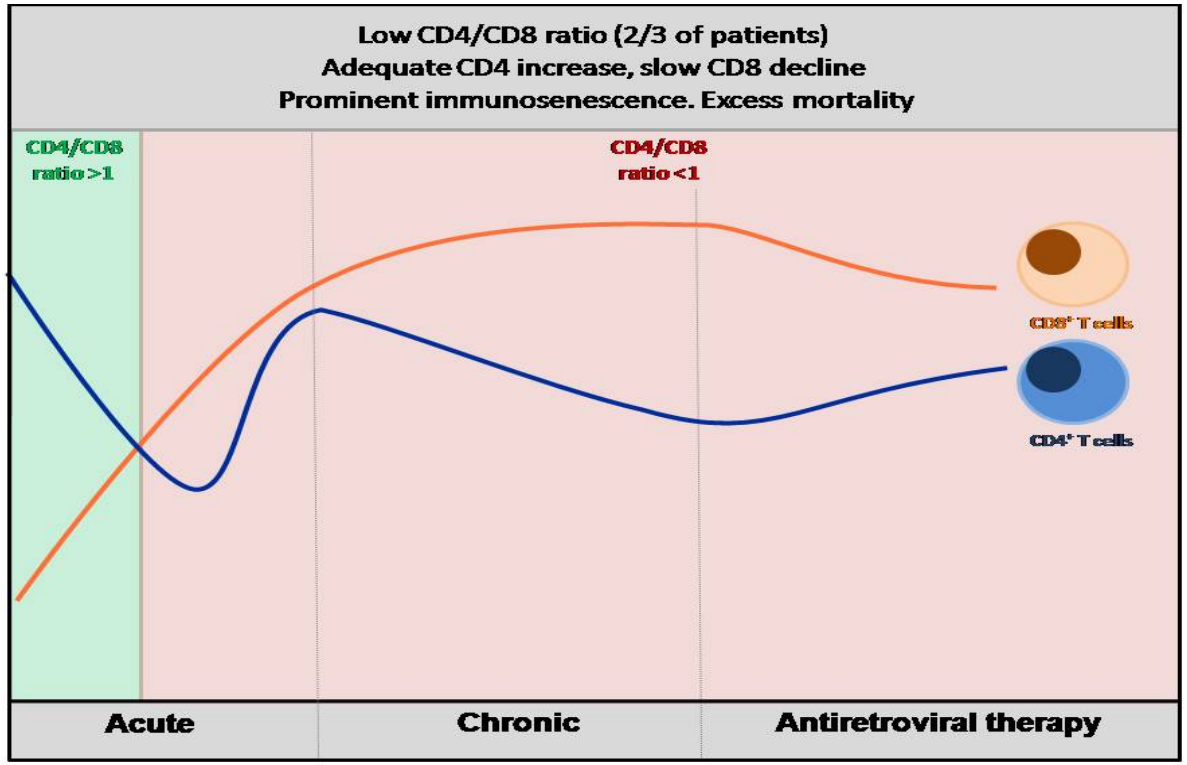
Neuhaus. JID 2010



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

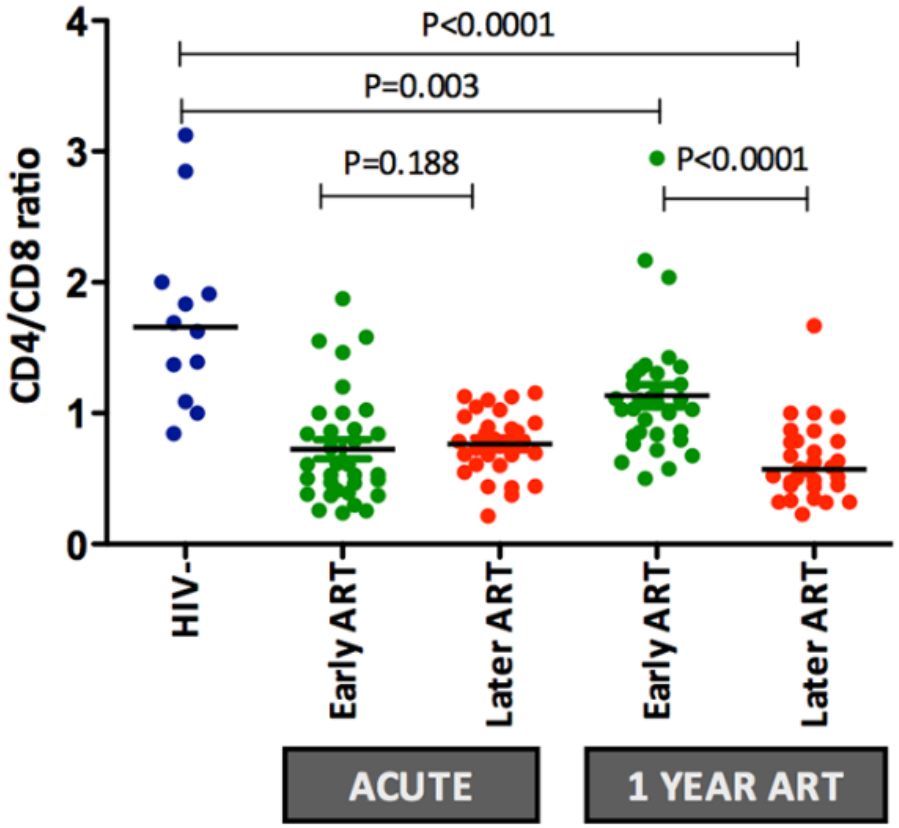
The CD4/CD8 ratio, a Proxy of Immunosenescence, Predicts Mortality During Treated HIV and is Impaired in 2/3 of Patients



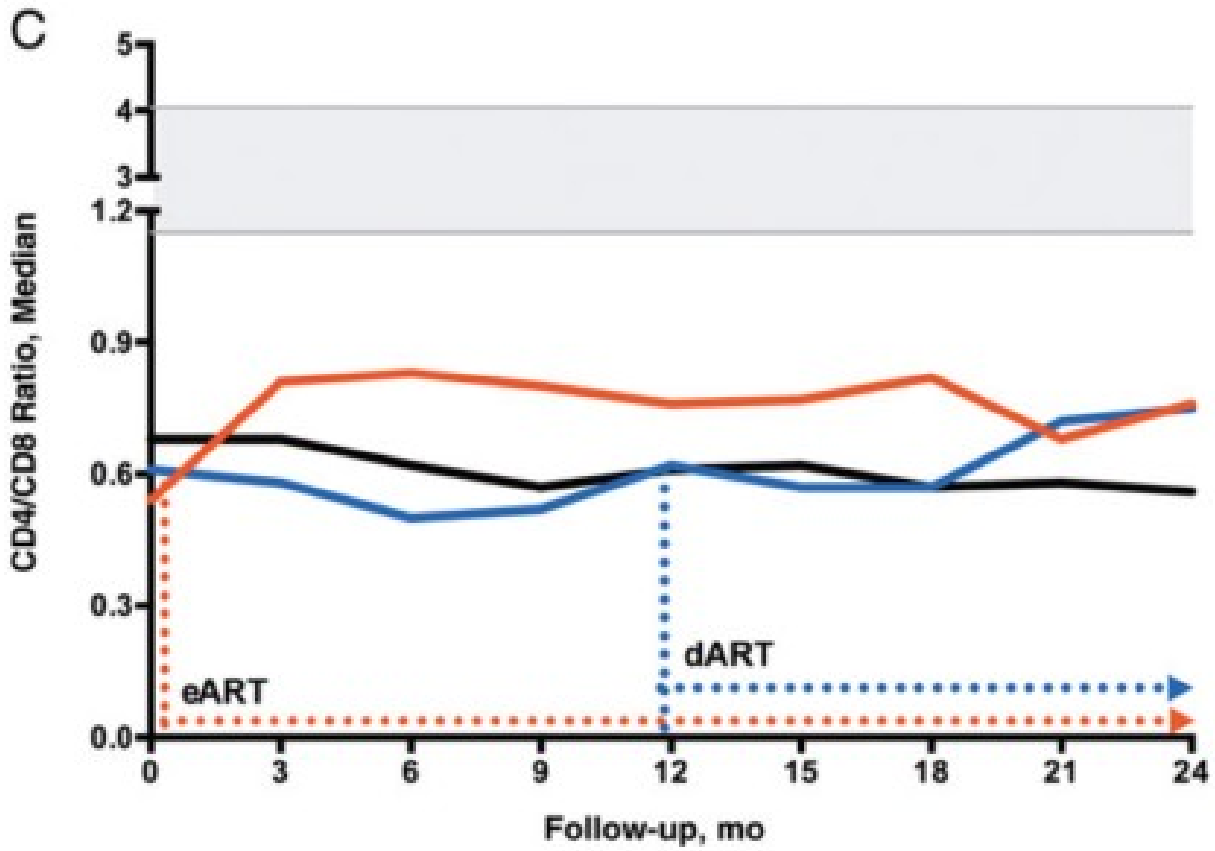


Serrano-Villar & Deeks. Lancet HIV 2015
(see also: Serrano-Villar, Plos Pathogens 2014, Mussini, Lancet HIV 2016

Very Early ART Initiation Improves but do not Normalize Inflammatory Markers



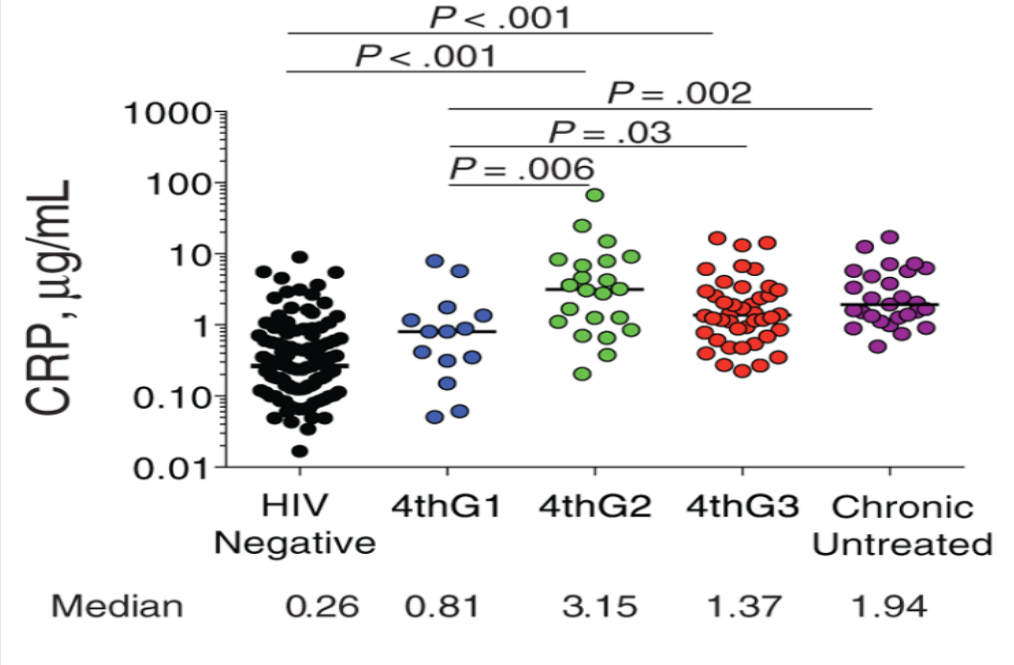
Serrano-Villar. Plos Pathogens 2014



Cao. CID 2016

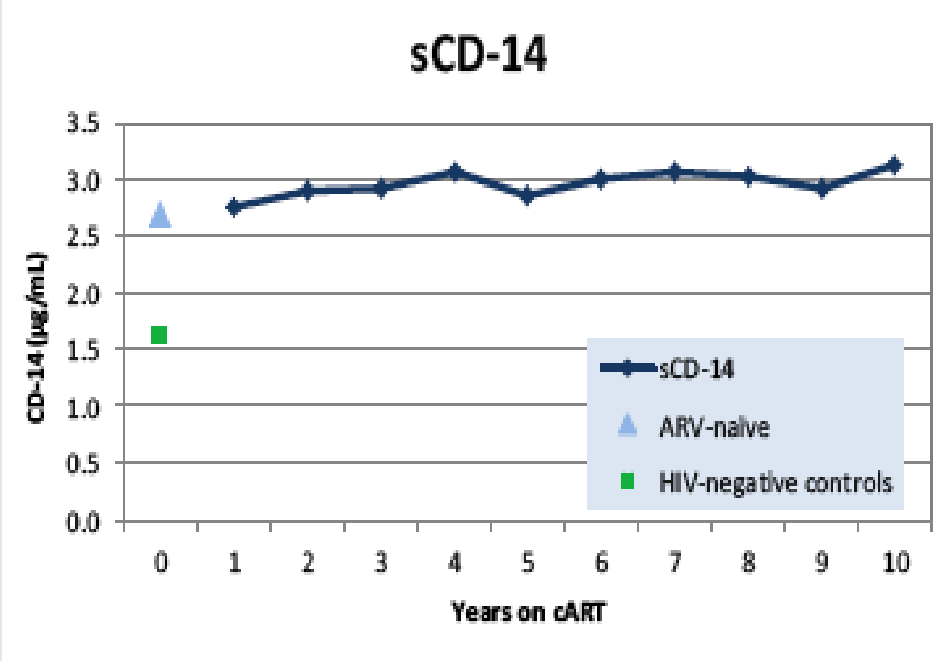
Very Early ART or Long-Term ART Improves but do not Normalize Inflammatory Markers

Inflammation Persists Despite Early Initiation of ART in Acute HIV Infection



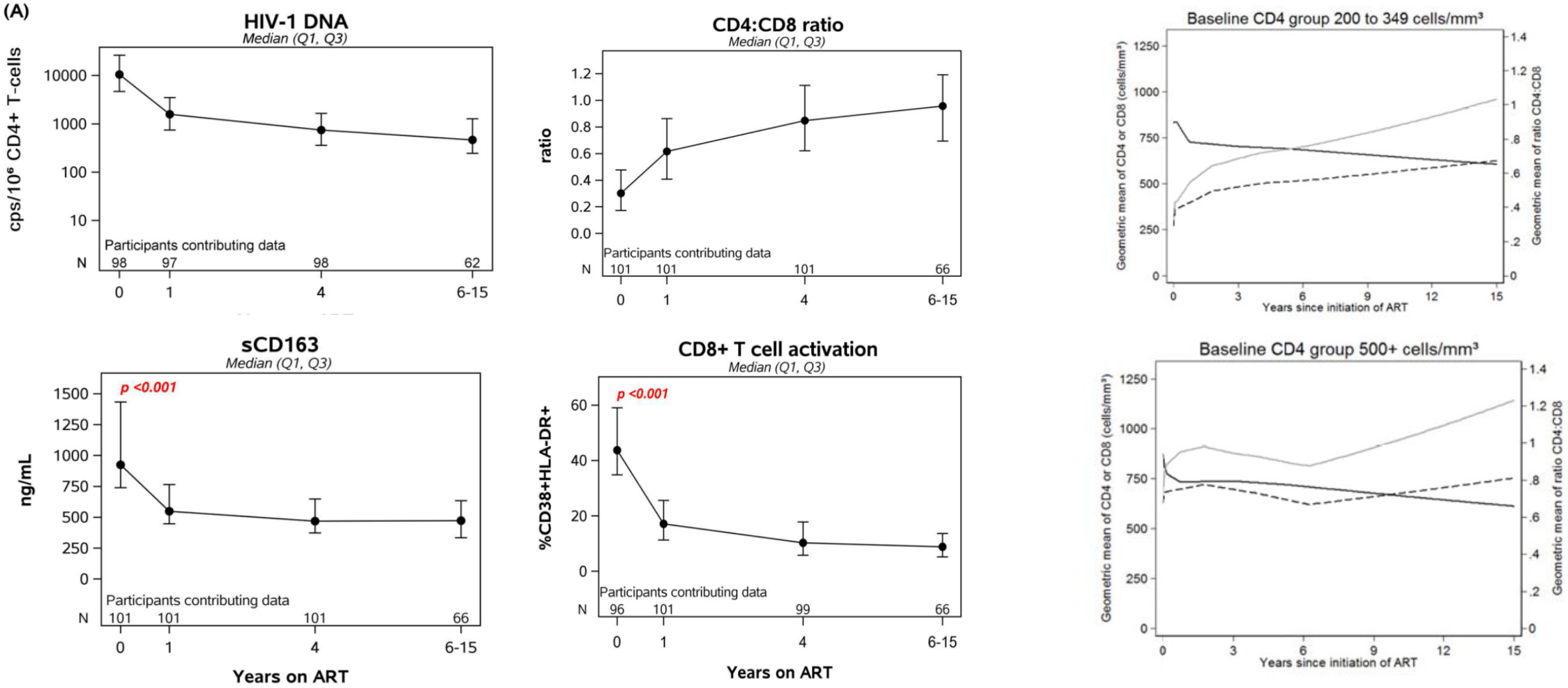
Sereti. CID 2017

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



Lichtenstein. CROI 2015

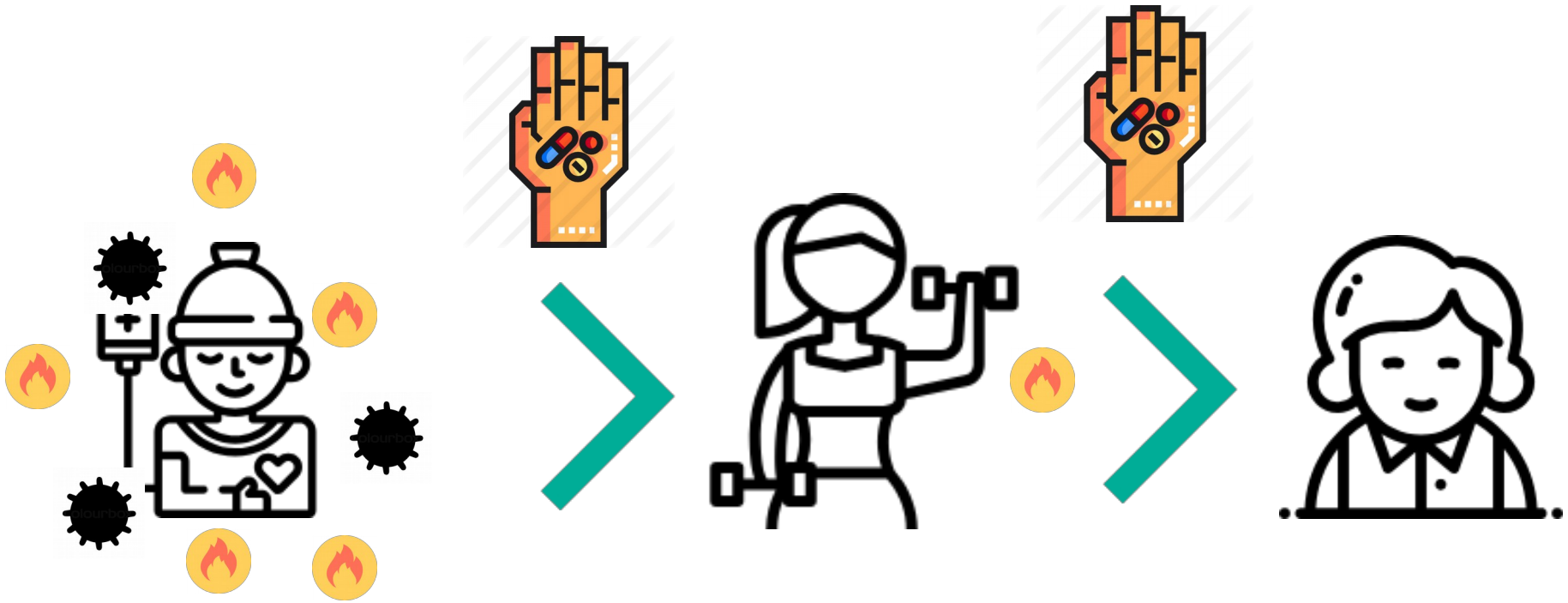
But… Most Biomarkers Improve Slowly During Long-Term Triple ART, especially if ART is Initiated Early



Gandhi. Plos Pathogens 2017

Hughes. AIDS 2018

Does ART fully restore health?



Personal communication

What is the source of inflammation?

Immune Activation As a Tree

Leaves

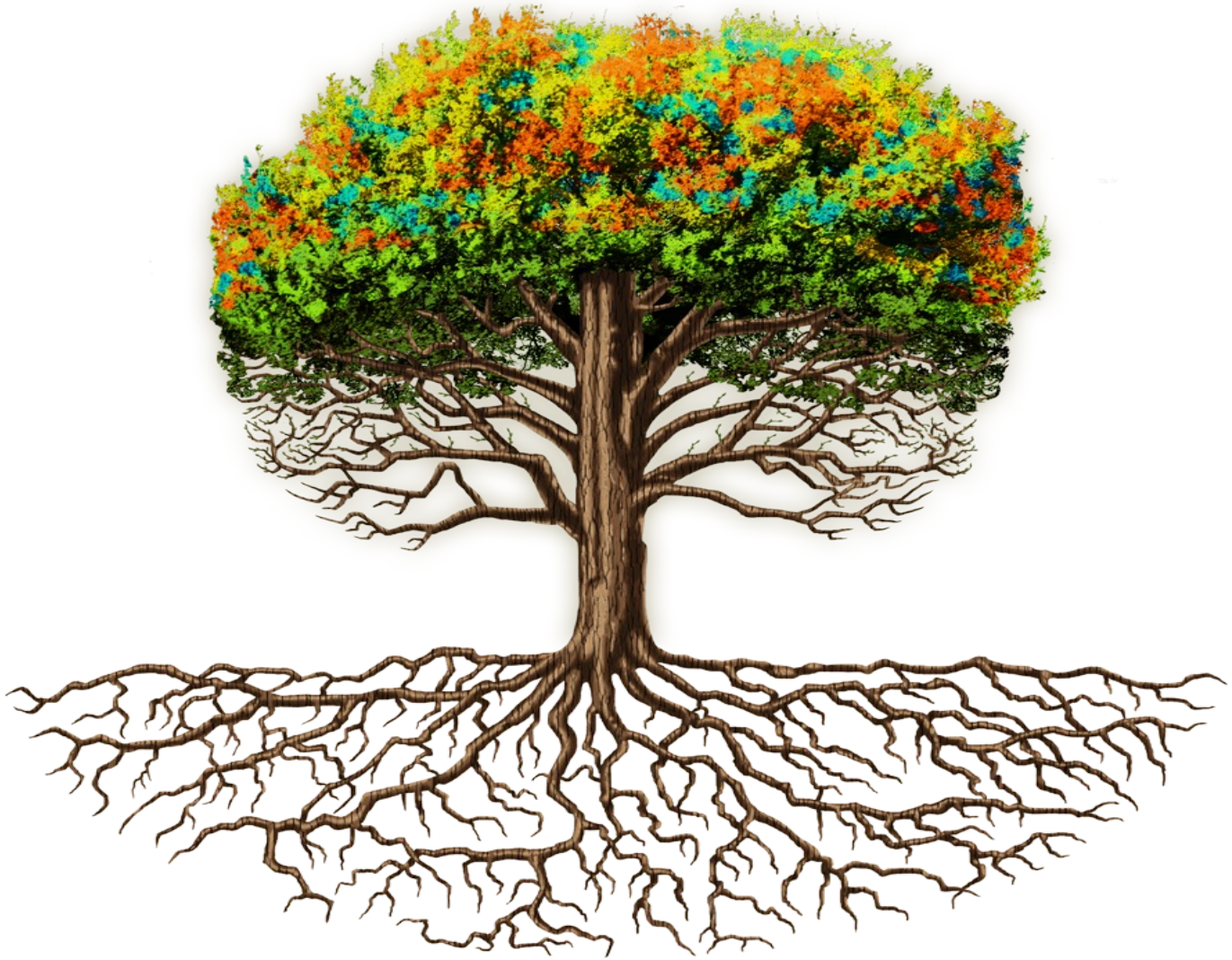
End-organ diseases

Branches

IL-6 / Inflammation
D-dimer / Coagulation
Lymphoid Fibrosis

Roots

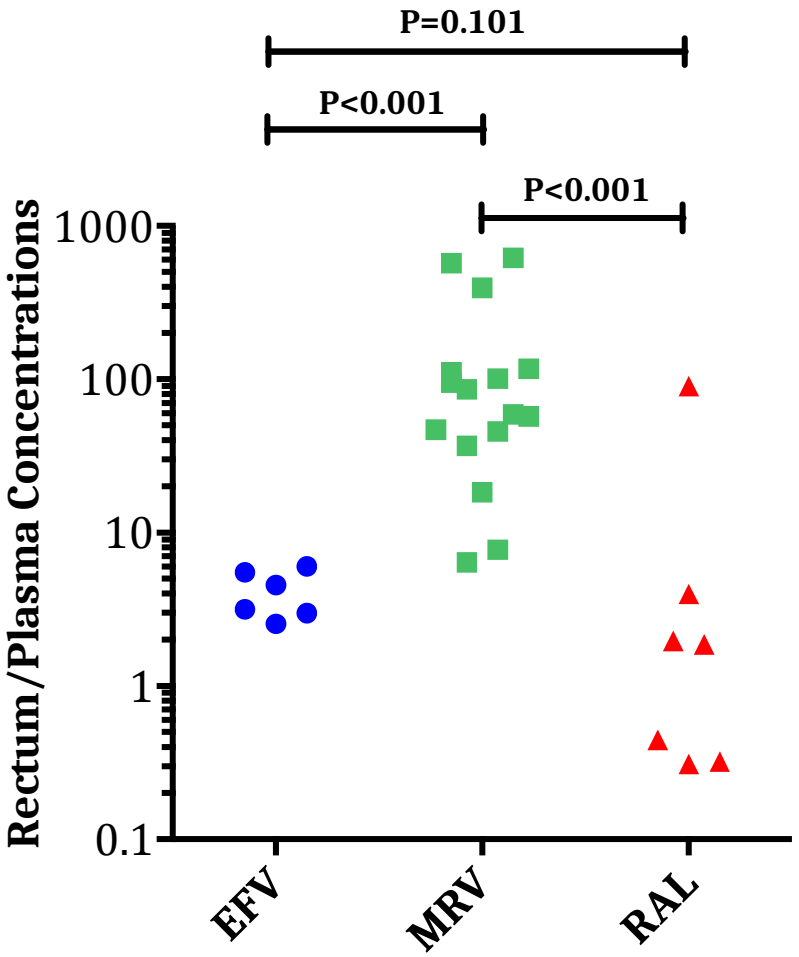
HIV reservoirs
CMV
Microbial translocation



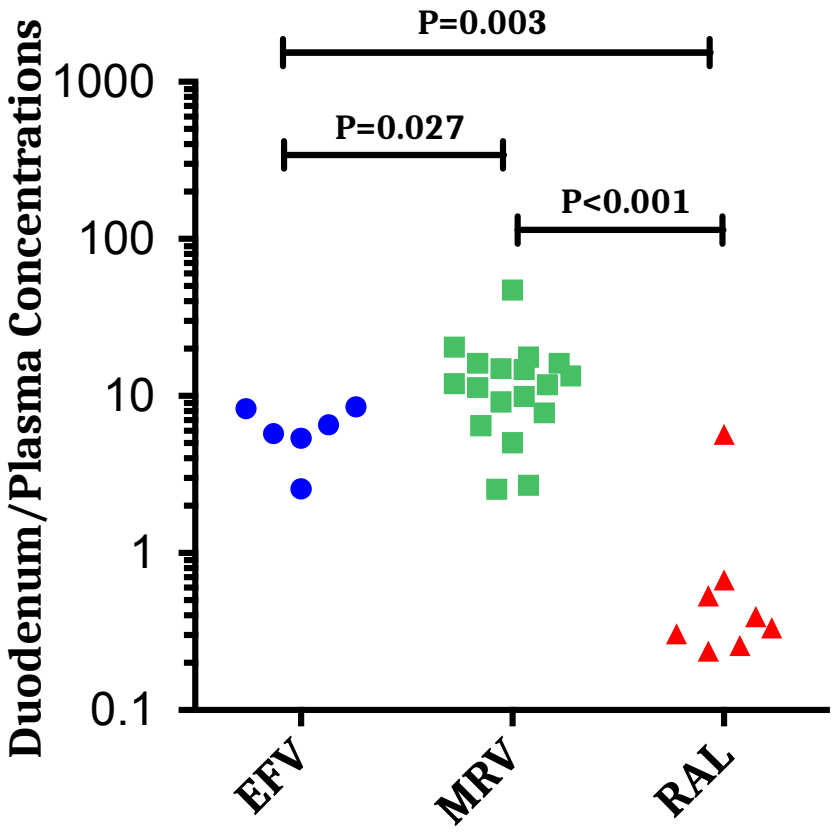
Slide from Peter Hunt

Variable penetration of ARV in tissue

Drug distribution to colon



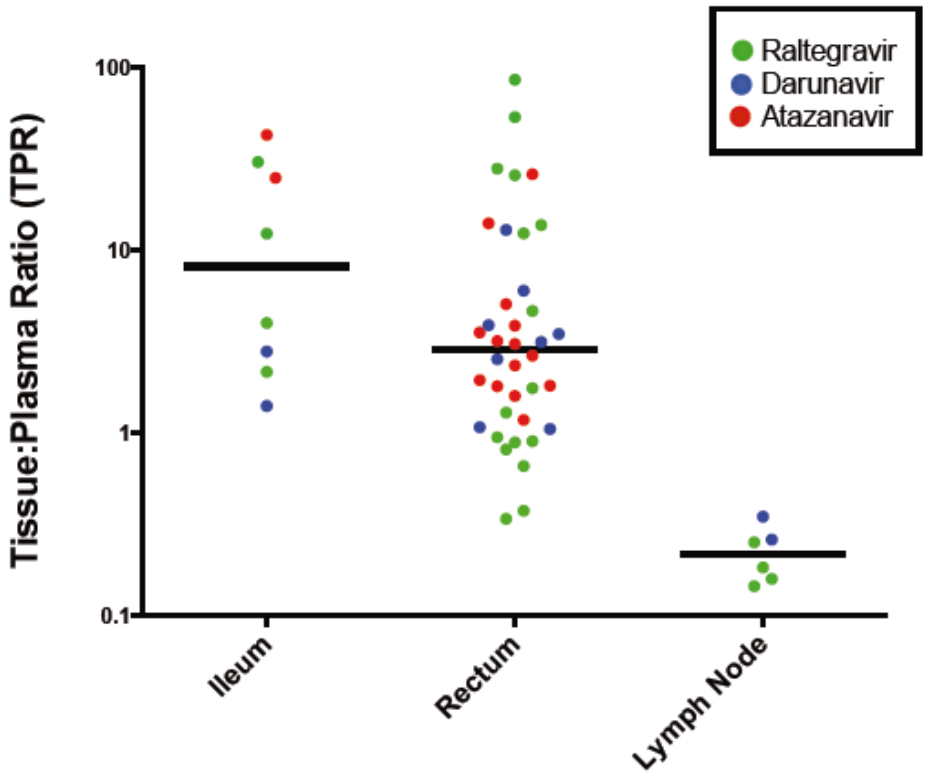
Drug distribution to duodenum



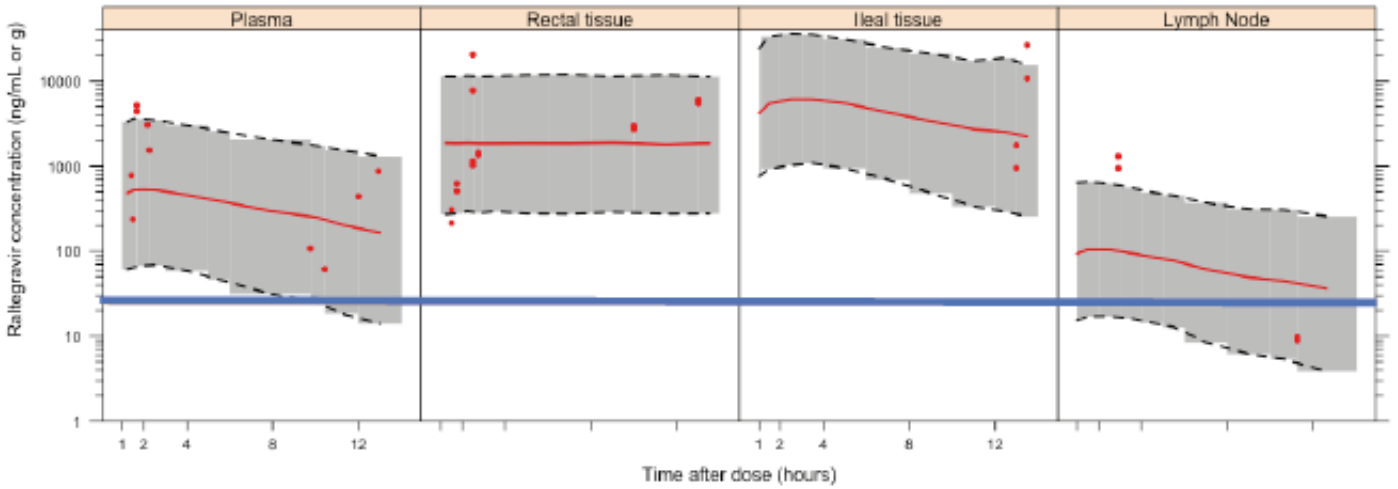
Serrano-Villar. PLoS Pathogens 2016

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).

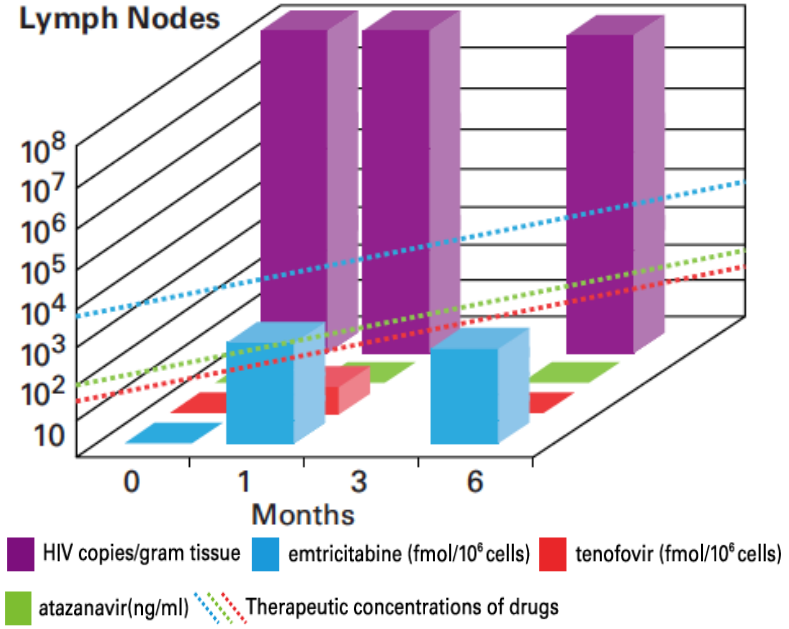
Lee. CROI 2017 (abstract #407)

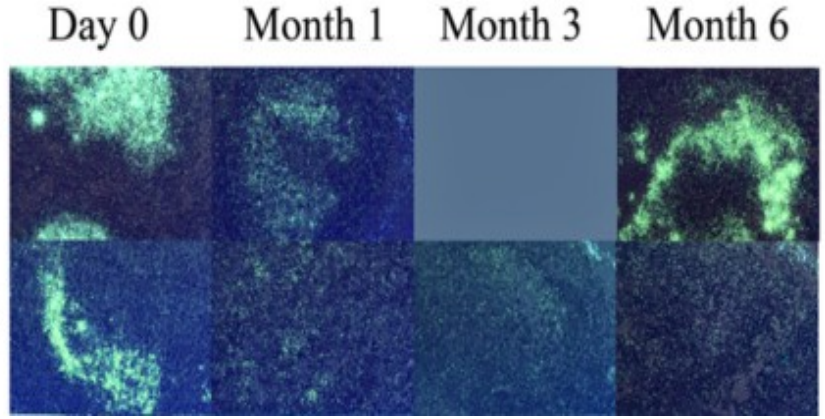
Variable penetration of ARV in tissue

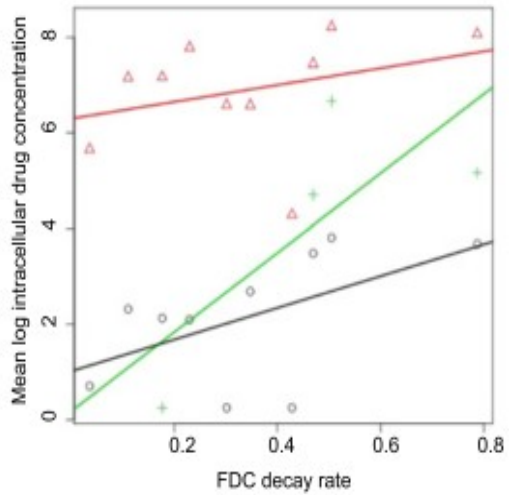
PNAS

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

Courtney V. Fletcher[a], Kathryn Staskus[b,1], Stephen W. Wietgrefe[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]







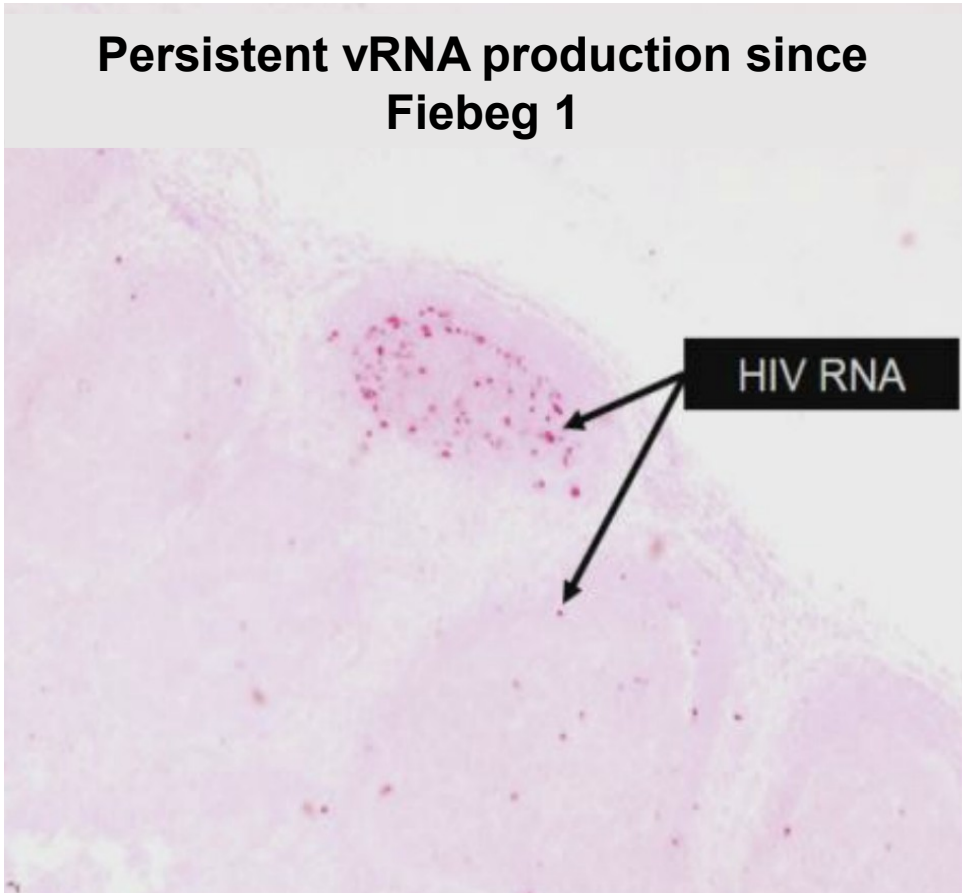
Fletcher, 19th CROI, Seattle 2012

Fletcher, PNAS 2014

(see also Lorenzo-Redondo, Nature 2016)

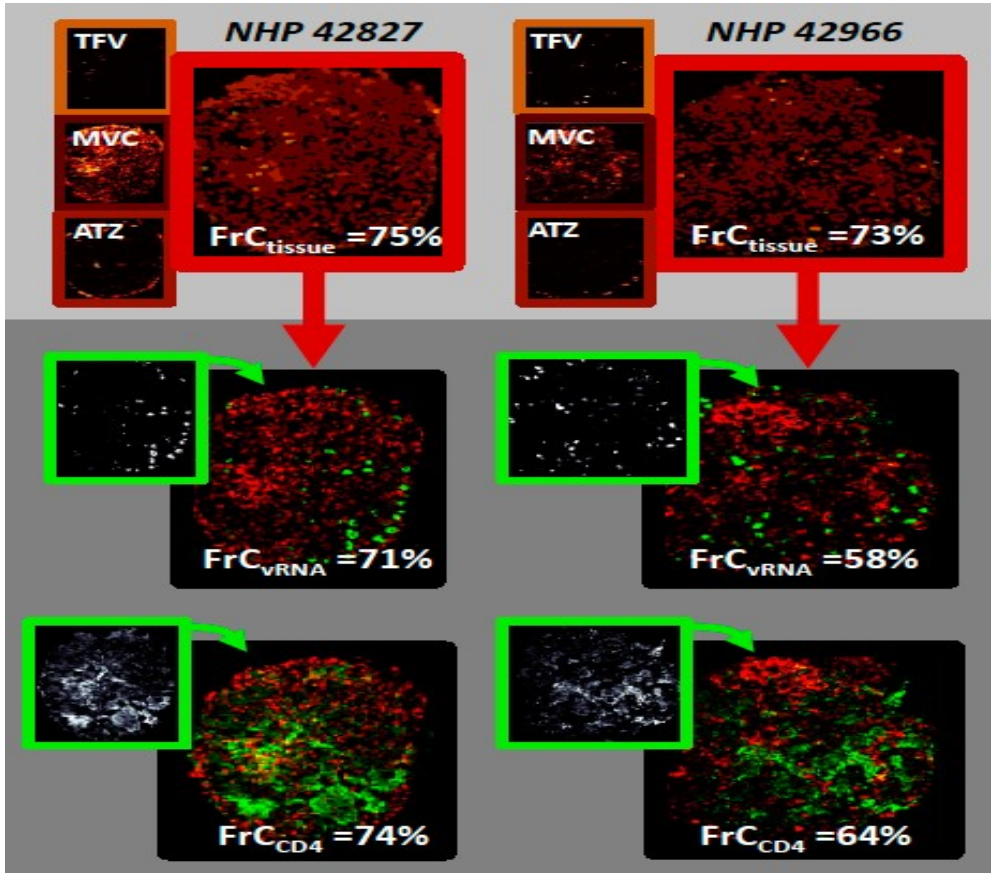
Ongoing viral replication and subtherapeutic ART concentrations in lymph nodes

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



Kroon. CROI 2018. Abstract #66

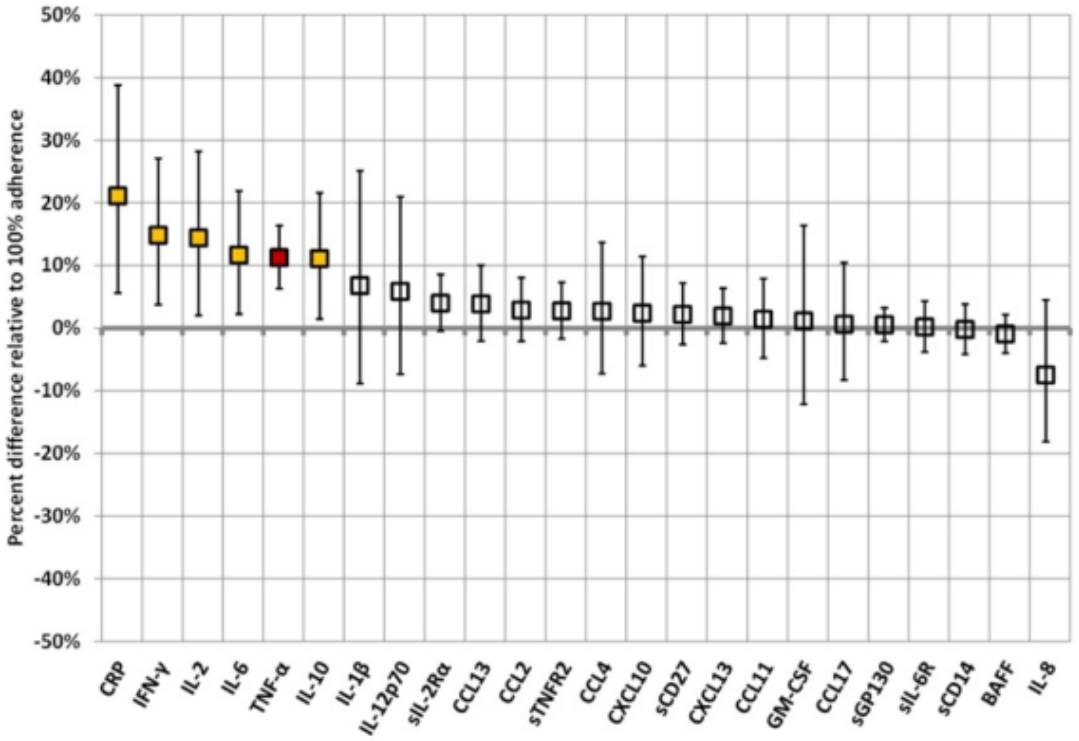
See also: #79 Bachman, Blips y HIV-DNA; #71 Rasmussen



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).



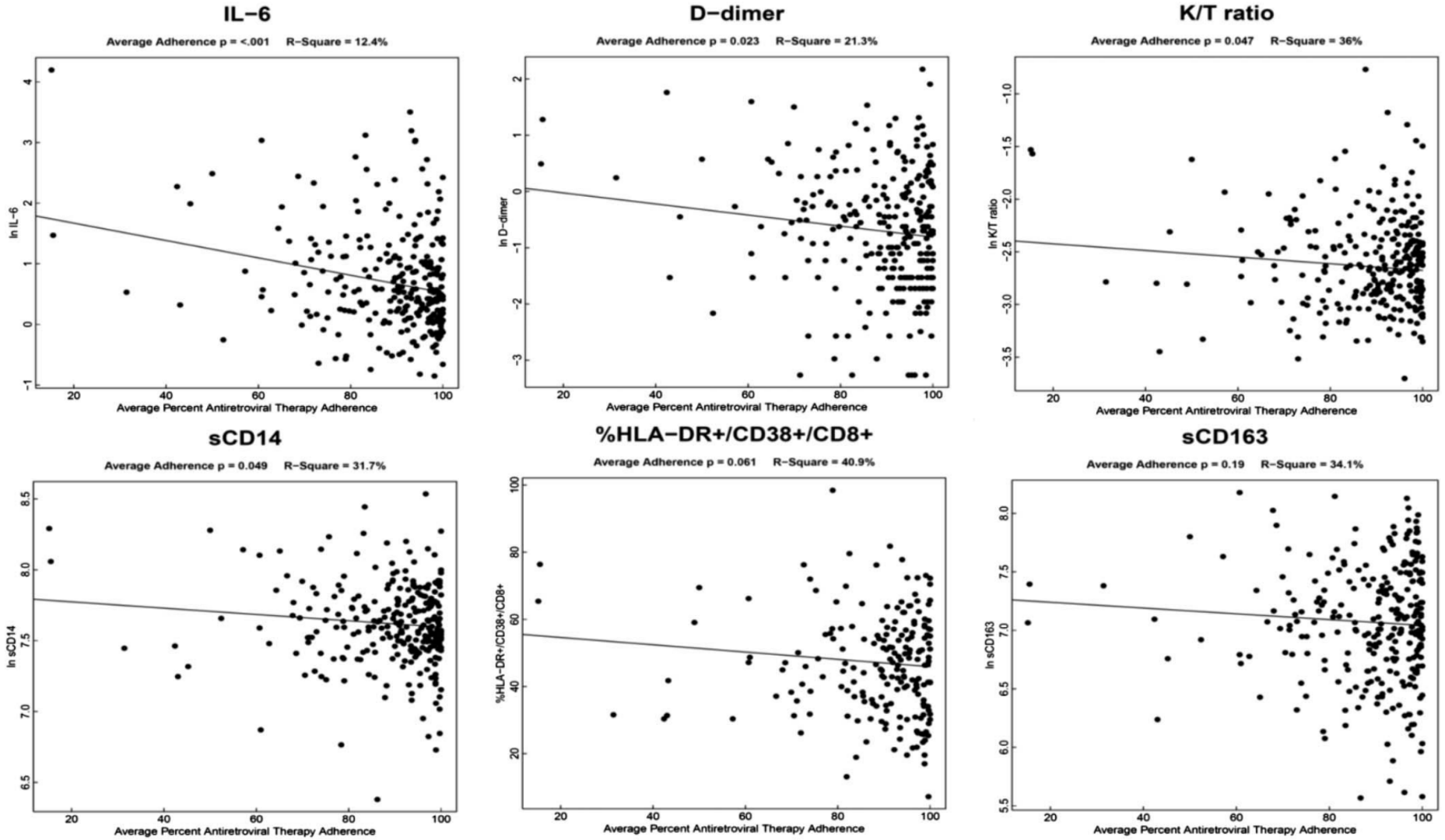
Abreviaturas: BAFF, factor activador de las células B; CCL, quimioquinas C-C ligando; CXCL quimioquinas CXC ligando; GM-CSF, factor estimulante de granulocitos y macrófagos ; IFN-■, interferón gamma; IL, interleucina; sCD14, CD14 soluble; sCD27, CD27 soluble; sgp130, glicoproteína soluble 130; sIL-2R✓,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

	<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: IFN-■, interferón gamma; IL, interleucina; TNF-✓, factor de necrosis tumoral ✓lpha; CRP, proteína C reactiva.

Castillo-Mancilla. Clin Infect Dis 2016

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



Castillo-Mancilla. JAIDS 2018

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

	Full Model For <400 copies/mL*				Full Model For <40 copies/mL*			
Biomarker	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.

Castillo-Mancilla. JAIDS 2018

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

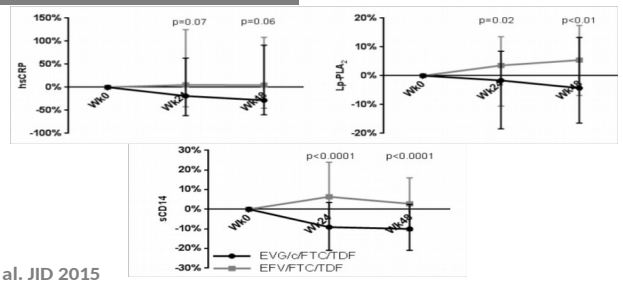
To be Defined: Likely Stronger Effects of INSTI-based First-Line ART

Effects of Fist-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

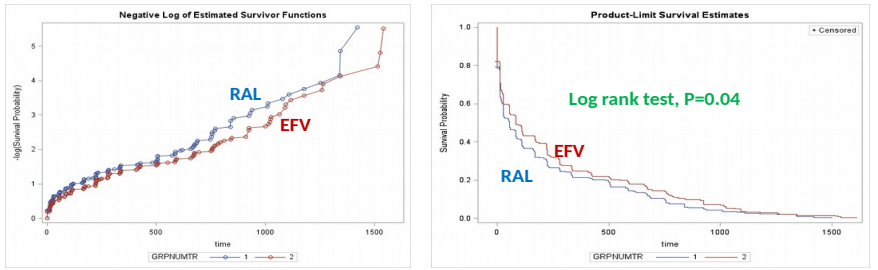
Monocyte activation (sCD14, sCD163), systemic (sTNF-RI, IL-6, hsCRP) and vascular inflammation (Lp-PLA2



Hileman et al. JID 2015

Hileman. JID 2015

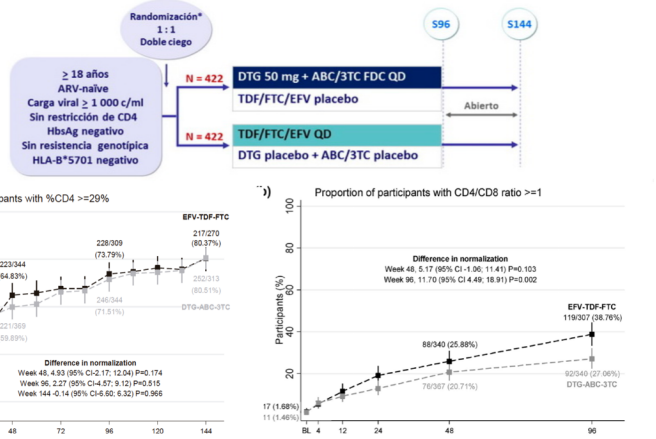
Raltegravir Normalized the CD4/CD8 Ratio Faster than Efavirenz in STARTMRK trial



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

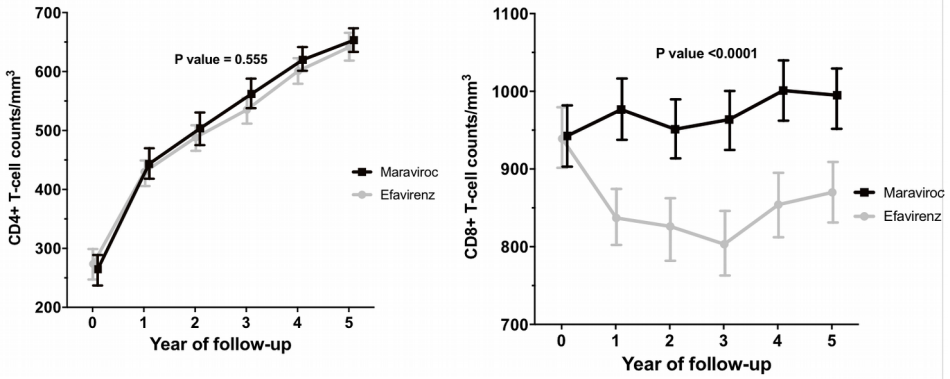
Serrano-Villar. JAC 2016

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

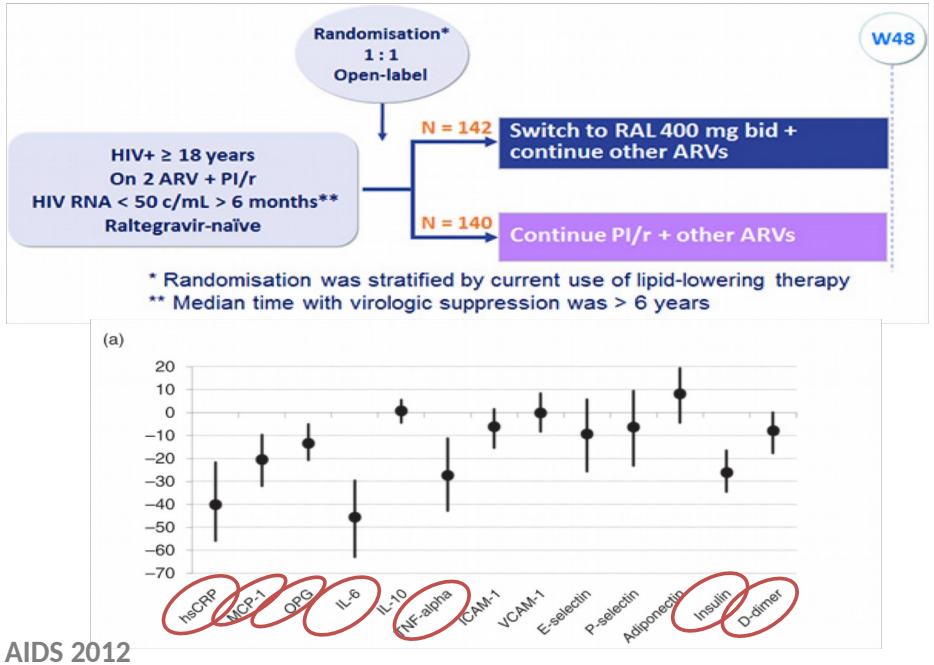
The effects of maraviroc versus efavirenz in combination with zidovudine/lamivudine on the CD4/CD8 ratio in treatment-naïve HIV-infected individuals



Serrano-Villar. Antimic Agent Chemother 2017

… and in Switching

Impact of switching from PI to raltegravir on cardiovascular biomarkers

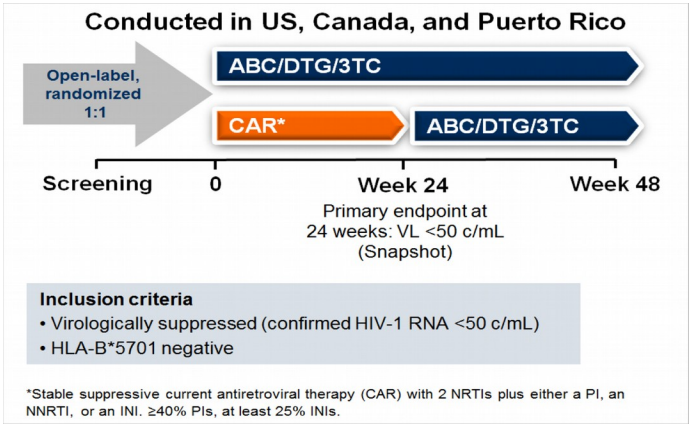


Martínez. AIDS 2012

Inflammatory markers improved after swithching to raltegravir

Martínez. AIDS 2012

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



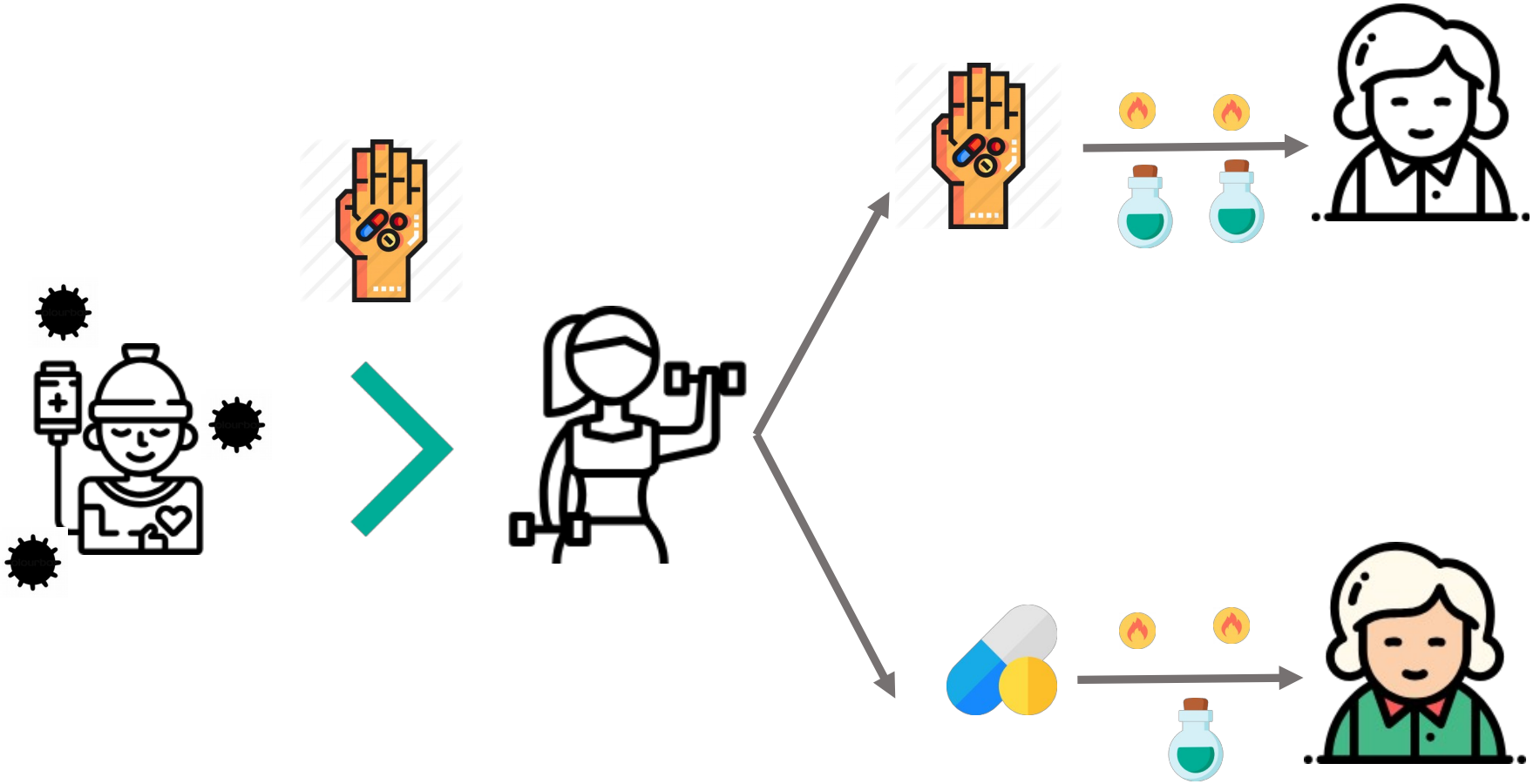
C-reactive protein (hs-CRP), interleukin-6 (IL-6), D-dimer, soluble vascular cell adhesion molecule (sVCAM), soluble CD14 and CD163 (sCD14, sCD163), and intestinal fatty acid–binding protein (I-FABP) levels were measured as secondary endpoints

Inflammatory markers improved after swithching 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



Personal communication

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

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

Andrew Carr[1,2]*, Jennifer Hoy[3,4], Anton Pozniak[5]

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.

Carr. Plos Medicine 2012

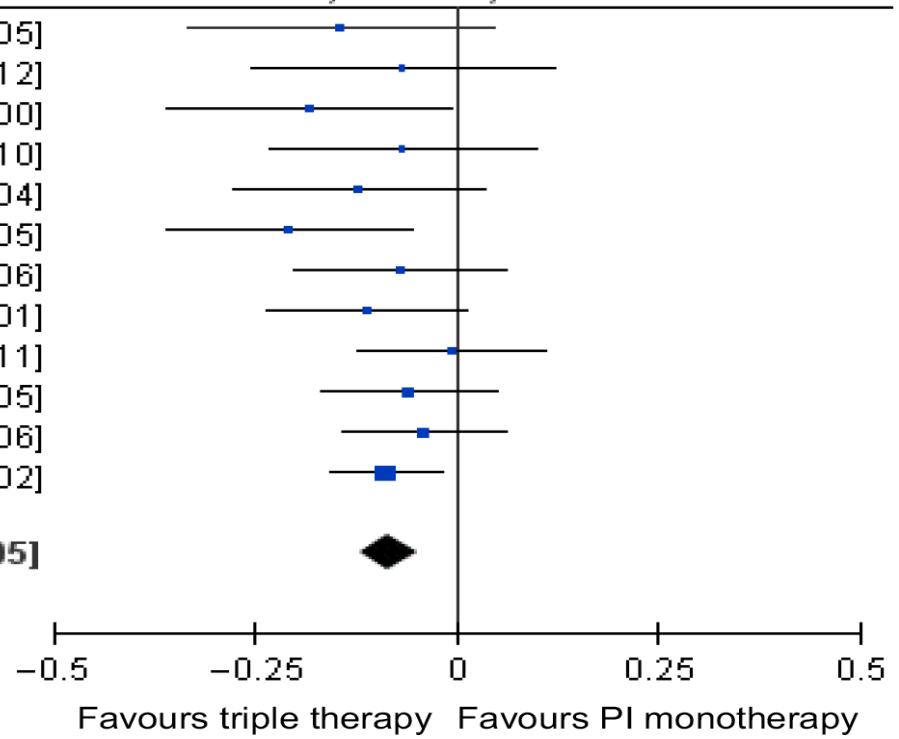
MONOTHERAPY META-ANALYSIS
Switch equals failure

A

Study or Subgroup	PI/r monotherapy Events	Total	Triple therapy Events	Total	Weight	Risk Difference IV, Random, 95% CI
OK Pilot	17	21	20	21	3.4%	−0.14 [−0.33, 0.05]
KalMo	24	30	26	30	3.6%	−0.07 [−0.25, 0.12]
KRETA	29	44	37	44	4.0%	−0.18 [−0.36, −0.00]
Monarch	14	15	15	15	4.5%	−0.07 [−0.23, 0.10]
MODAT	37	51	44	52	5.1%	−0.12 [−0.28, 0.04]
MOST	23	29	31	31	5.3%	−0.21 [−0.36, −0.05]
DREAM	63	98	69	97	7.3%	−0.07 [−0.20, 0.06]
MONOI	66	112	79	113	8.1%	−0.11 [−0.23, 0.01]
OK-04	77	100	76	98	9.2%	−0.01 [−0.12, 0.11]
MONET	88	127	97	129	10.5%	−0.06 [−0.17, 0.05]
KALESOLO	73	87	87	99	12.4%	−0.04 [−0.14, 0.06]
PROTEA	118	137	129	136	26.5%	−0.09 [−0.16, −0.02]
Total (95% CI)		**851**		**865**	**100.0%**	**−0.08 [−0.12, −0.05]**
Total events	629		710			

Heterogeneity: tau² = 0.00; χ = 7.19, df = 11 (P = 0.78); I^2 = 0%

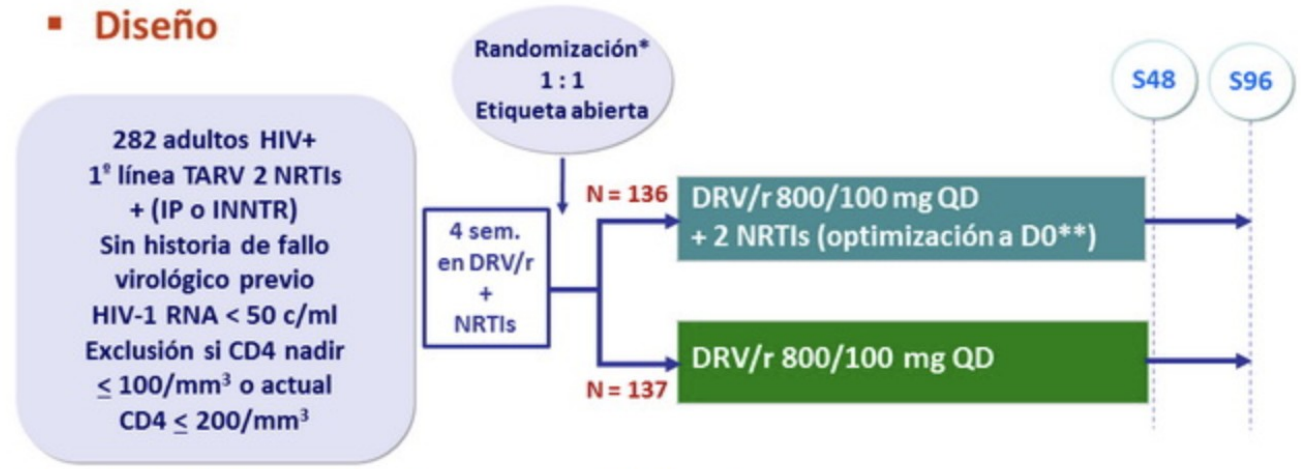
Test for overall effect: Z = 4.62 (P < 0.00001)



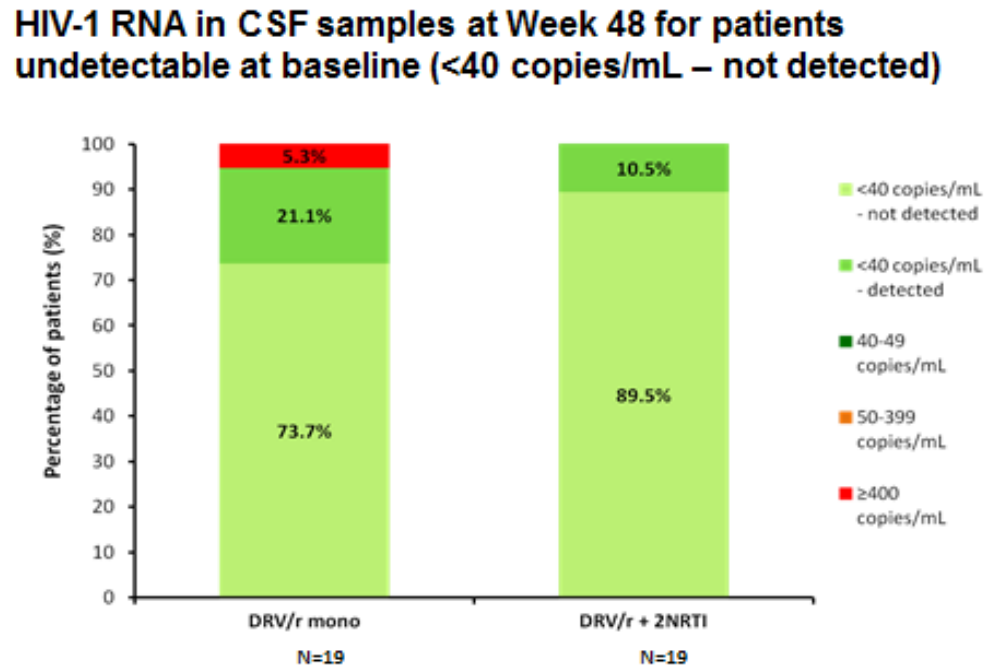
"PI/r monotherapy showed a higher risk of plasma HIV-1 RNA elevations"

Arribas. HIV Med 2016

PROTEA Study
HIV-1 RNA in CSF samples at Week 48



* La randomización fue estratificada por status anti-HCV (+ o -)
** TDF, ABC o ZDV + 3TC o FTC

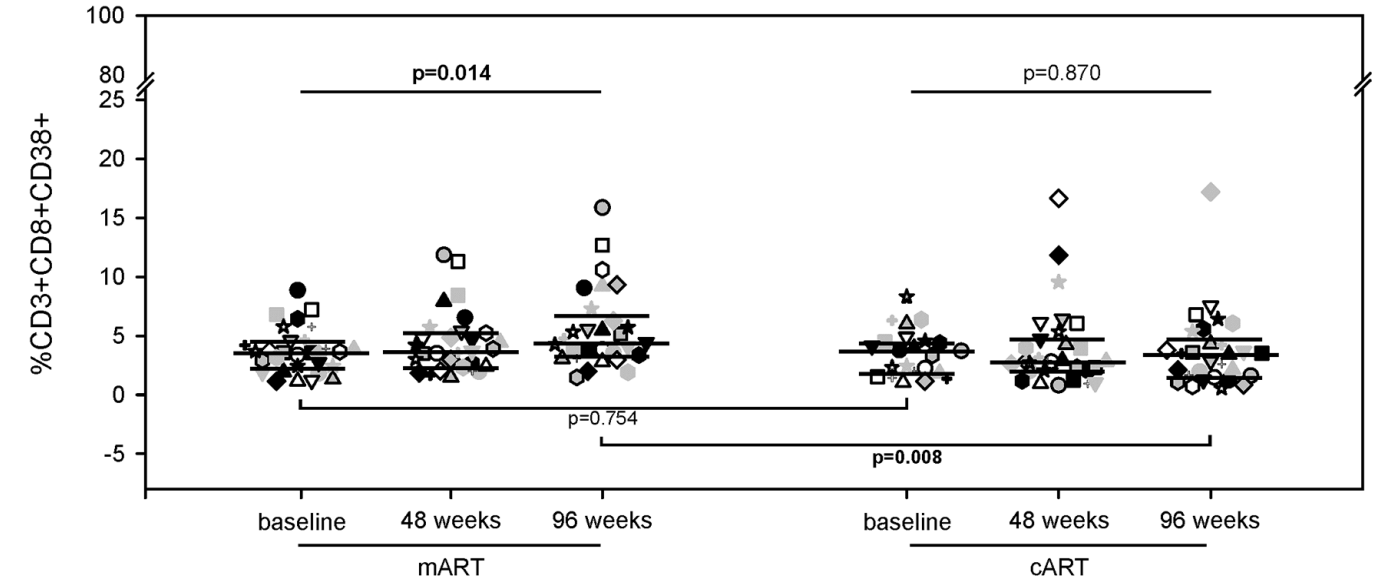


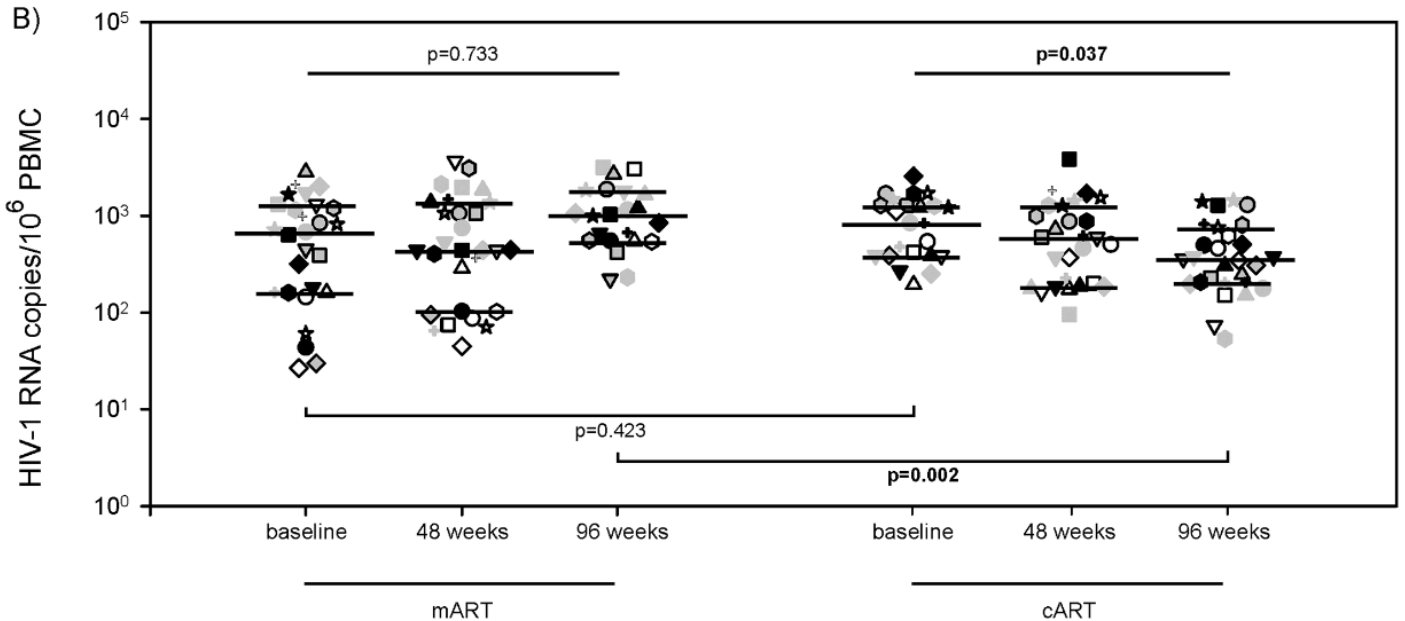
There were 2 patients with HIV-1 RNA <40 copies/mL (target detected) at baseline in the CSF. Both patients had HIV RNA <40 copies/mL (target not detected) at Week 48.

- Dos pacientes en la rama monoterapia con CD4 nadir < 200/mm^{3}desarrollaron viremia tanto en LCR como en plasma, con un caso sintomático.

Antinori. AIDS 2015

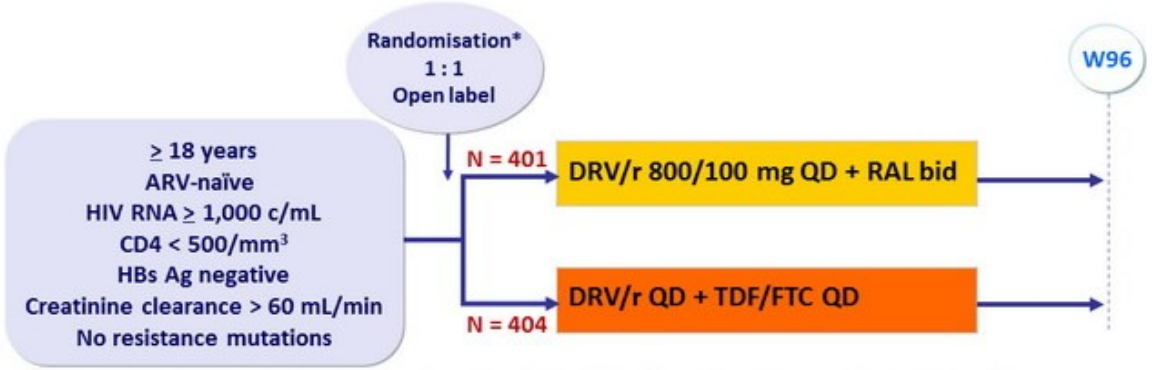
Immune Activation in mART-treated and cART-treated patients

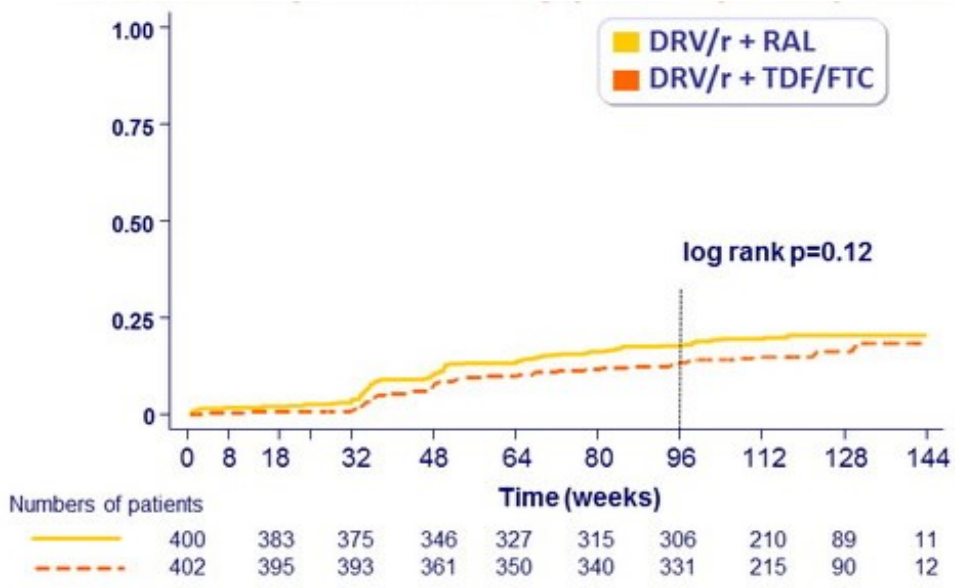




Petrara. PLoS One 2017

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/mm^3 at treatment start.
- Despite a low rate of virological failure in both arms, emergence of resistance mutations was higher in the raltegravir group.

Raffi. Lancet 2014

Telomere Length Change

RAL: Raltegravir. DRV/r: Darunavir/ritonavir. TDF: Tenofovir Disoproxil Fumarate.
FTC: Emtricitabine.

"In the predictive model the **only variables associated with telomere gain at W96 were treatment with TDF/FTC**, **younger age** (mean difference 0.001, p=0.042) and **no current use of alcohol at baseline** (mean difference 0.048, p=0.038)"

Estella-Ascariz. JID 2018

Participant characteristics

	RAL + DRV/r N=104	TDF/FTC + DRV/r N=97	p-value
Age, (yr) *	38.7 (10.4)	38.6 (10.8)	0.961
Female, n(%)	11 (10.6)	11 (11.3)	0.862
Smoking (Currently), n(%)	35 (33.7)	39 (40.2)	0.417
Alcohol use (Currently), n(%)	4 (3.8)	10 (10.3)	0.197
Time since HIV diagnosis (yr) *	2.2 (3.3)	2.0 (2.8)	0.699
Baseline HIV-1 RNA (log_{10} cp/mL) *	4.7 (0.7)	4.7 (0.6)	0.729
HIV RNA < 50 copies/mL at week 96, n(%)	99 (95.2)	89 (91.8)	0.322
Median time to HIV RNA < 50 copies/mL, (weeks)	8 (4-12.6)	18 (9.4-24.1)	**<0.001**
CD4 Baseline (cells/mm^3)*	332.6 ± 133.3	315.3 ± 122.2	0.339
CD4 Change (cells/mm^3)*	265.52 ± 159.6	253.40 ± 167.4	0.602
CD8 Baseline (cells/mm^3)*	948.2 ± 442.7	924.6 ± 500.2	0.507
CD8 Change (cells/mm^3)*	-123.9 ± 442.2	-124.9.6 ± 350.4	0.987
CD4/CD8 Baseline*	0.5 ± 0.8	0.4 ± 0.2	0.536
CD4/CD8 Change*	0.4 ± 0.8	0.4 ± 0.3	0.333
CD4/CD8 >0.4 at week 96, n(%)	94 (90.4)	83 (85.6)	0.558
CD4/CD8 >1 at week 96, n(%)	35 (33.7)	30 (30.9)	0.918

Estella-Ascariz. JID 2018

Telomere Length Change

RAL: Raltegravir. DRV/r: Darunavir/ritonavir. TDF: Tenofovir Disoproxil Fumarate.
FTC: Emtricitabine.

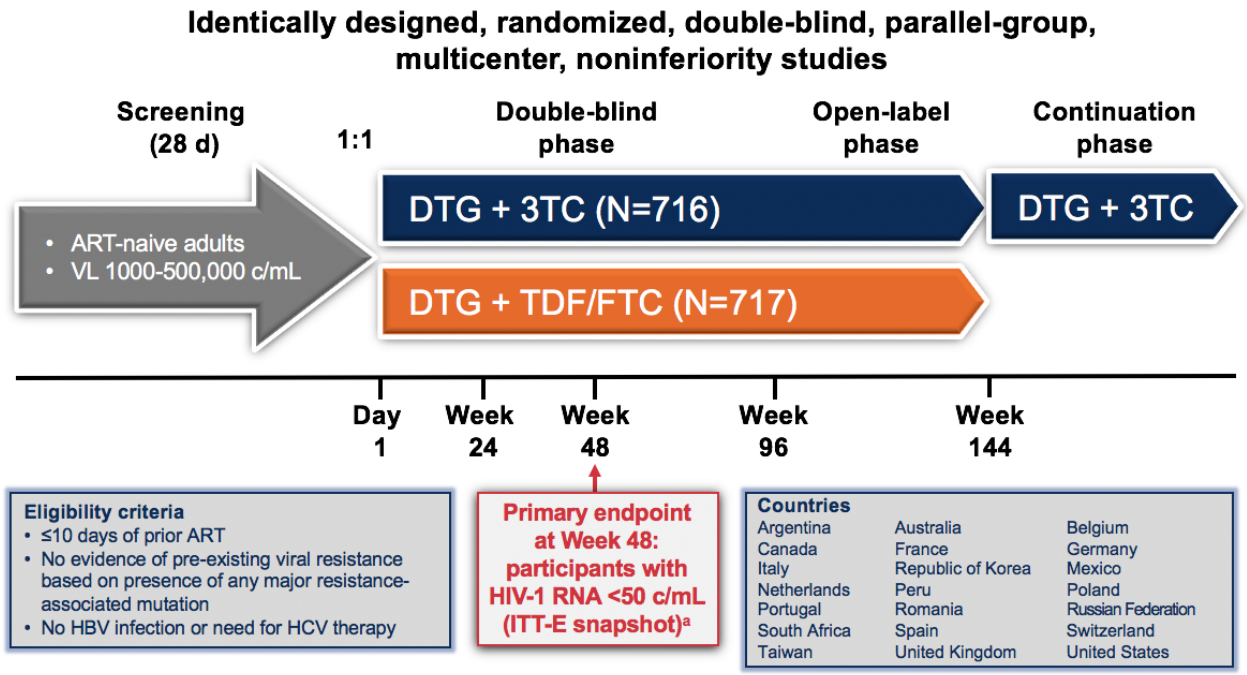
Estella-Ascariz. JID 2018

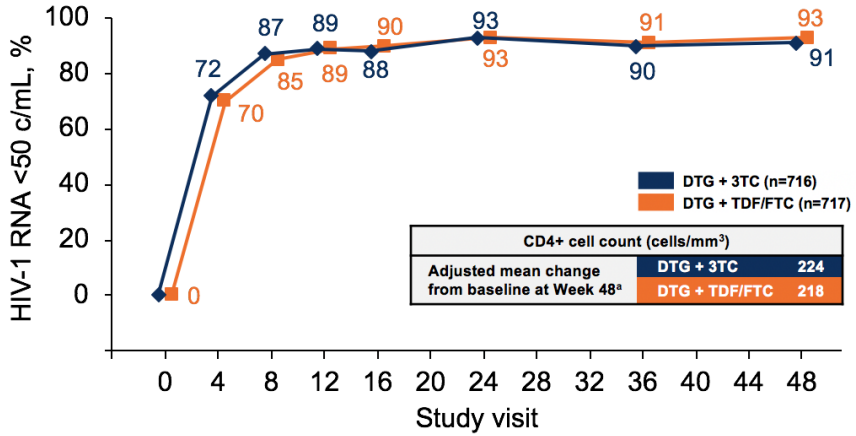
Telomere Length Change

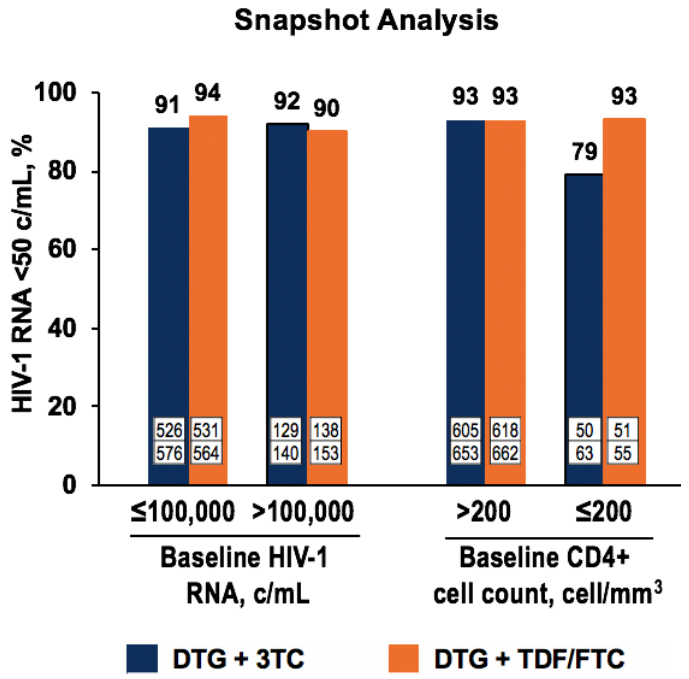
RAL: Raltegravir. DRV/r: Darunavir/ritonavir. TDF: Tenofovir Disoproxil Fumarate.
FTC: Emtricitabine.

Estella-Ascariz. JID 2018

GEMINI 1-2
DTG+3TC vs. DTG+TDF/FTC





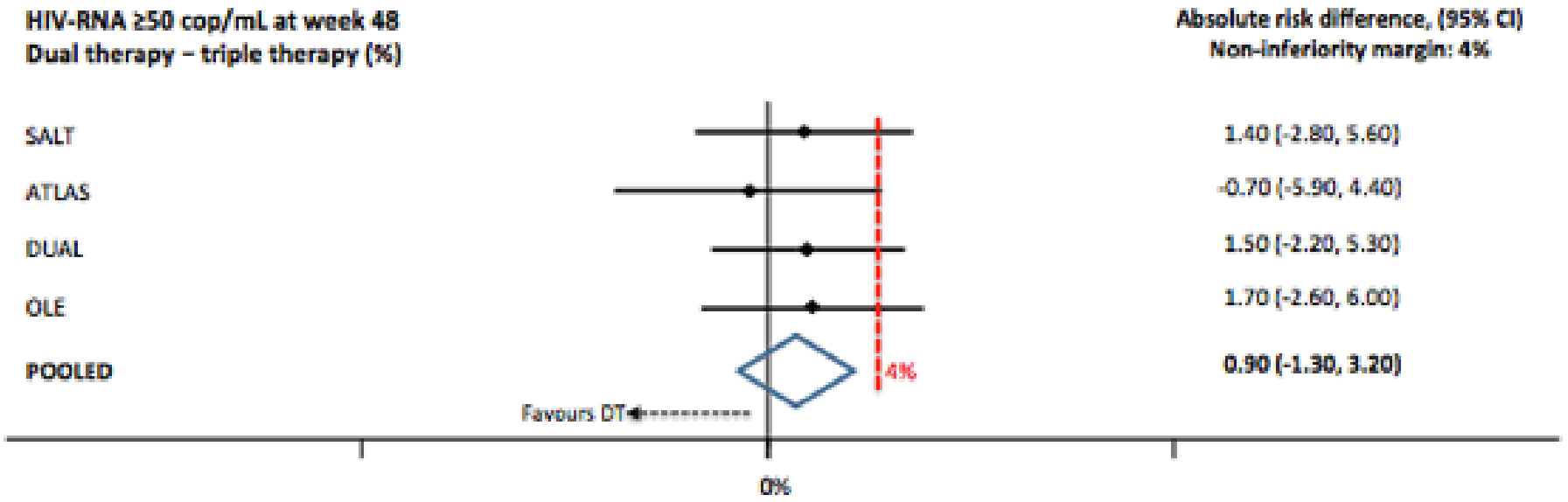


Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

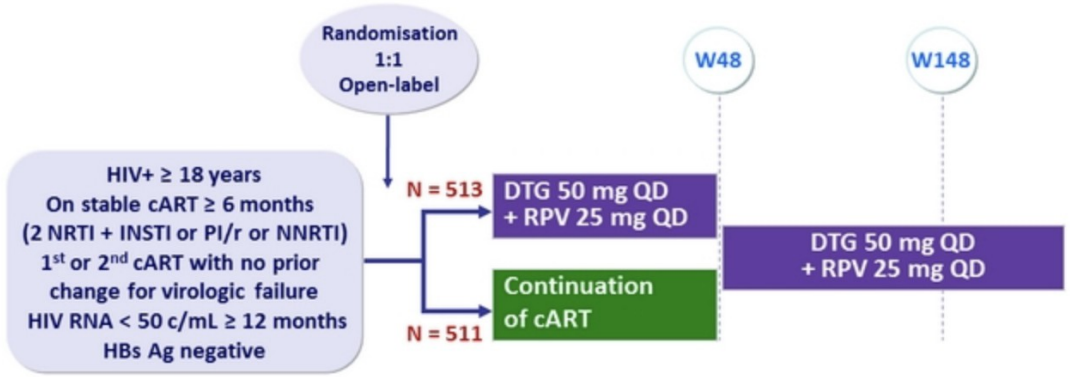
Individual Patient-Data Metanalysis of Dual Therapy RCT

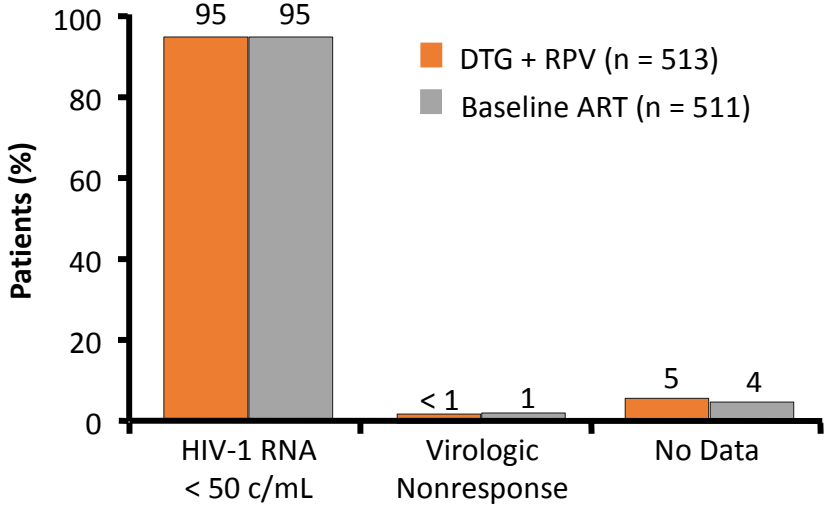
At 48w, 4% of patients on DT vs. 3.04% on TT had HIV-RNA ≥50 cop/mL

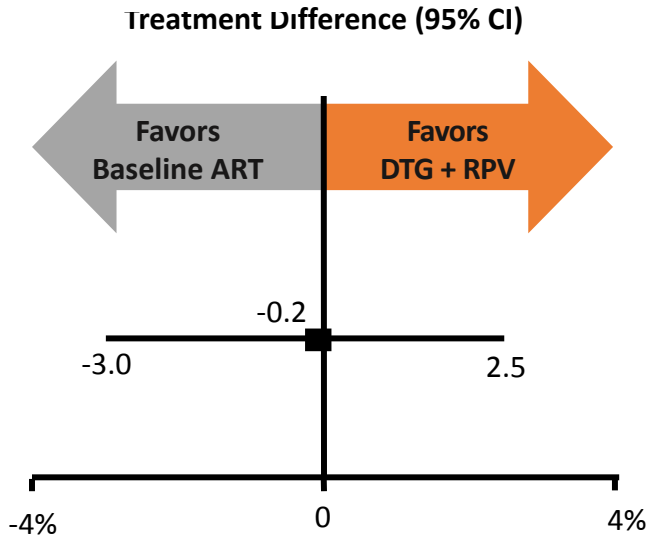
Difference 0.9% (95%CI, -1.3% to 3.2%)



SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV in Patients With No Previous VF





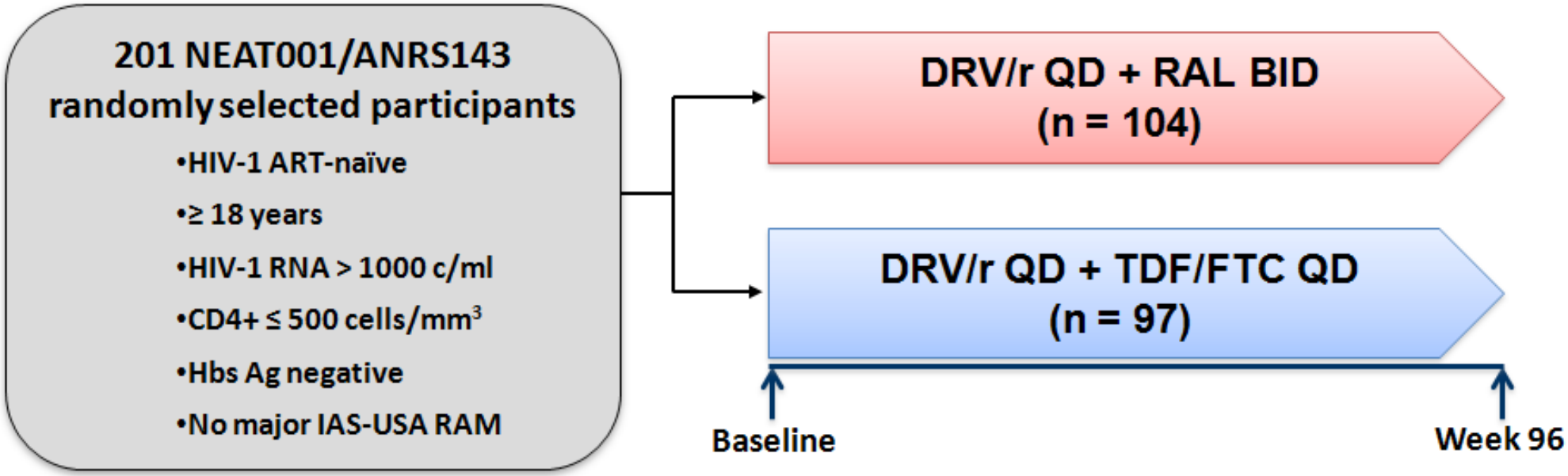


Llibre JM, et al. Lancet. 2018;391:839-849.

Slide credit: clinicaloptions.com
arv-trials.com

Blood telomere lengths after FTC/TDF or RAL as First-Line ART in ANRS143/NEAT001

- 201 NEAT001/ANRS143 participants were randomly selected among those from whom stored blood samples were available (baseline and week 96).



Estella-Ascariz. JID 2018

SWORD Studies: Inflammation (Week 48)

Table 3. Atherogenesis and Inflammation Biomarkers: Change From Baseline to Week 48 (Pooled SWORD Data)

Biomarker	DTG + RPV n	DTG + RPV Mean (median [range])	CAR n	CAR Mean (median [range])	Week 48 difference, DTG+RPV – CAR (95% CI)
Inflammation					
C-RP, mg/L					
Baseline[a]	512	2.81 (1.3 [0.1, 34.4])	505	2.77 (1.3 [0.1, 33.8])	
Week 48	480	0.11 (0.0 [−32.7, 40.3])	482	0.47 (0.0 [−31.1, 96.0])	−0.36 (−1.2, 1.0)
IL-6, ng/L					
Baseline[a]	512	2.19 (1.6 [0.4, 15.1])	503	2.25 (1.57 [0.3, 34.5])	
Week 48	478	0.04 (−0.04 [−13.7, 25.8])	480	−0.12 (−0.05 [−32.8, 13.6])	0.16 (−0.2, 0.4)
Hypercoagulability					
D-dimer, nmol/L FEU					
Baseline[a]	504	1.87 (1.2 [1.0, 51.8])	496	1.80 (1.1 [1.0, 38.9])	
Week 48	463	−0.01 (0.0 [−19.9, 23.1])	466	−0.05 (0.0 [−37.8, 16.4])	0.04 (−0.28, 0.34)
Macrophage activation					
sCD163, µg/L					
Baseline[a]	509	590.48 (537.7 [176.0, 2036.9])	501	601.79 (555.4 [176.0, 1934.4])	
Week 48	477	57.99 (52.8 [−856.4, 1052.1])	477	54.10 (26.0 [−999.6, 1434.2])	3.89 (−22.4, 206.3)
Monocyte activation					
sCD14, ng/mL					
Baseline[a]	510	1703.31 (1677.5 [50.0, 3688.4])	502	1698.60 (1696.3 [50.0, 3381.8])	
Week 48	479	419.09 (363.7 [−1374.0, 3112.4])	479	778.15 (773.8 [−1571.3, 7569.2])	−359.06 (−451.7, 2325.5)
Endothelial dysfunction					
sVCAM-1, µg/L					
Baseline[a]	512	1933.50 (1894.6 [478.3, 4066.6])	503	1957.52 (1871.1 [776.1, 6106.9])	
Week 48	479	−2.43 (−21.5 [−3006.4, 9596.4])	480	63.57 (16.1 [−3983.1, 7594.6])	−66.00 (−190.8, 4180.9)
Fatty acid metabolism					
FABP2, ng/mL					
Baseline[a]	512	2.97 (2.3 [0.2, 23.7])	501	2.92 (2.37 [0.3, 19.3])	
Week 48	478	−2.13 (−1.5 [−22.1, 2.7])	478	−1.47 (−1.0 [−14.2, 4.7])	−0.66 (−0.9, 0.3)

CI, confidence interval; C-RP, C-reactive protein; FABP2, fatty acid binding protein-2; FEU, fibrinogen equivalent unit; sCD14, soluble cluster of differentiation 14; sCD163, soluble cluster of differentiation 163; SD, standard deviation; sVCAM-1, soluble vascular adhesion molecule 1. [a]Baseline values are actual values.

Orkin. EACS 2017

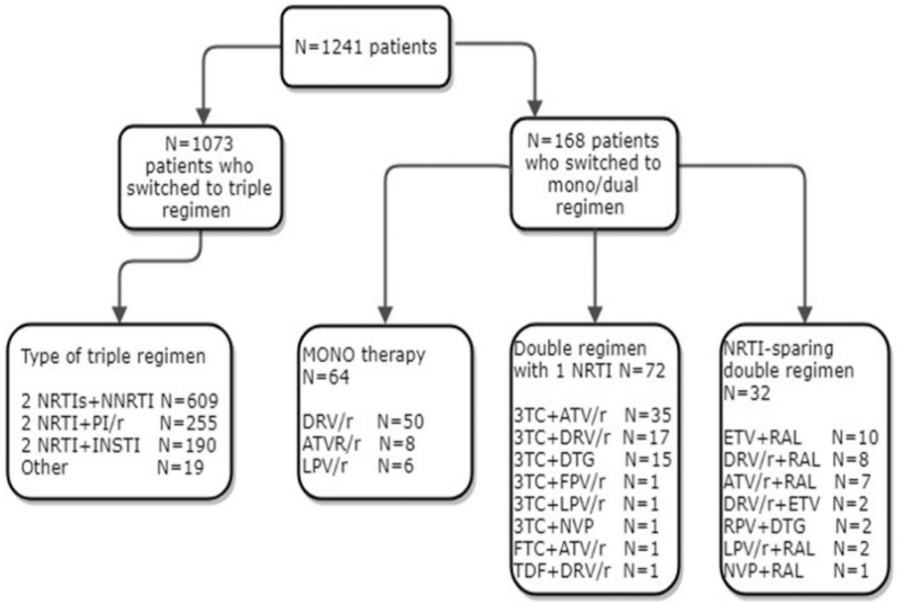
"No consistent pattern of change from baseline to week 48 or differentiation between the dolutegravir-rilpivirine group and the CAR group was observed for the inflammatory or cardiovascular biomarkers: interleukin-6, C-reactive protein, soluble vascular cell adhesion molecule-1, soluble CD14, soluble CD163, fatty acid binding protein-2, and d-dimer ***(data not shown)****".*

Llibre. Lancet Infect Dis 2017

RESEARCH ARTICLE Open Access

Switching to dual/monotherapy determines an increase in CD8+ in HIV-infected individuals: an observational cohort study

Cristina Mussini[1*], Patrizia Lorenzini[2], Alessandro Cozzi-Lepri[3], Giulia Marchetti[4], Stefano Rusconi[4], Andrea Gori[4], Silvia Nozza[5], Miriam Lichtner[6], Andrea Antinori[2], Andrea Cossarizza[7], Antonella d'Arminio Monforte[4] and for the Icona Foundation Study Group



Beta coefficient from fitting linear regression models

End-point: change del CD4/CD8 ratio (log10), CD8, CD4 at 12 months.

Every model is adjusted for: age, gender, mode of HIV transmission, Italian nationality, previous AIDS event, years of HIV infection, HCV co-infection, HIV-RNA and CD4 at cART initiation, CD4 and CD8 count at switch, reason for switch, months of viral suppression.

End-point: CD4/CD8 ratio (log10) change at 12 months	Beta	95% CI		P-value
Regimen after switch				
triple	ref			
mono/dual	-0.03	-0.06	-0.006	0.015
End-point: CD8 change at 12 months	**Beta**	**95% CI**		**P-value**
Regimen after switch				
triple	ref			
mono/dual	+89.7	+30.3	+149.1	0.003
End-point: CD4 change at 12 months	**Beta**	**95% CI**		**P-value**
Regimen after switch				
triple	ref			
mono/dual	-3.8	-39.7	+32.1	0.836

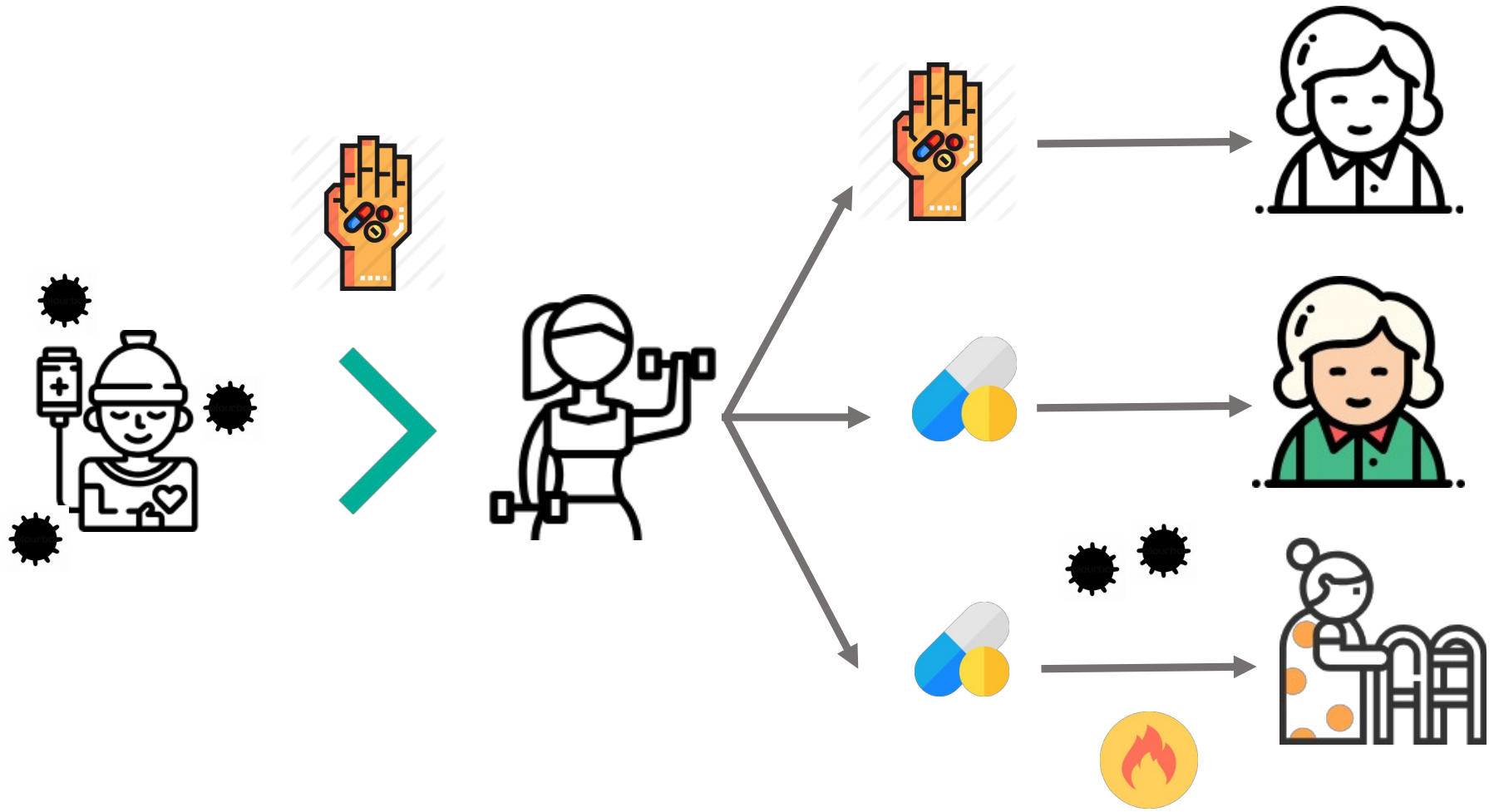
Do we really need to routinize the treatment with less than three drugs?

Current Nukes ……

- Are highly convenient
  - Can be administered in fixed dose combinations (Kivexa®, Truvada®, Descovy®) or as a single tablet regimen (Atripla®, Eviplera®, Stribild®, Triumeq®, Odefsey®, Genvoya®)
  - At any time of the day
  - With no food or fluid requirements
  - With long half-lives and high permisiveness
  - Also in special situations (TB, pregancy, HBV,…)
- Have no significant interactions
- Have a favorable safety profile
- In triple ART protect against the development of mutations

"It pains me to tell you this, but it ain't broke."

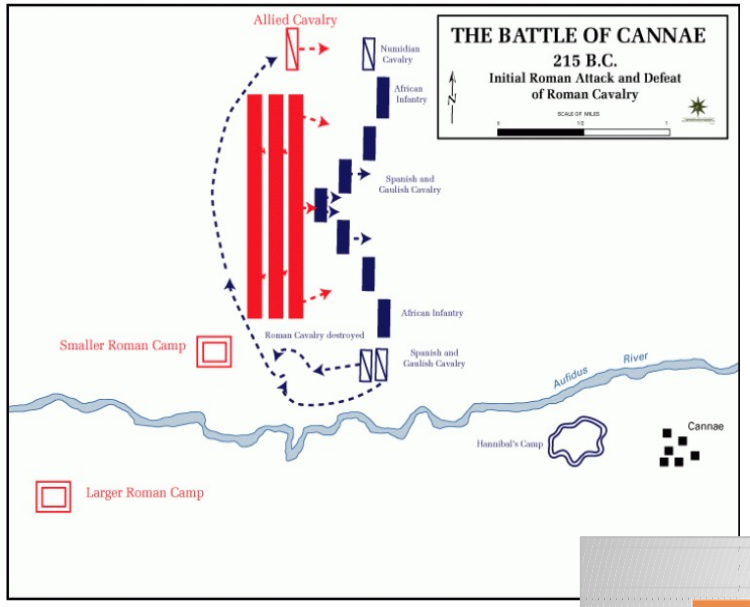
Rationale for dual therapy benefits and risks

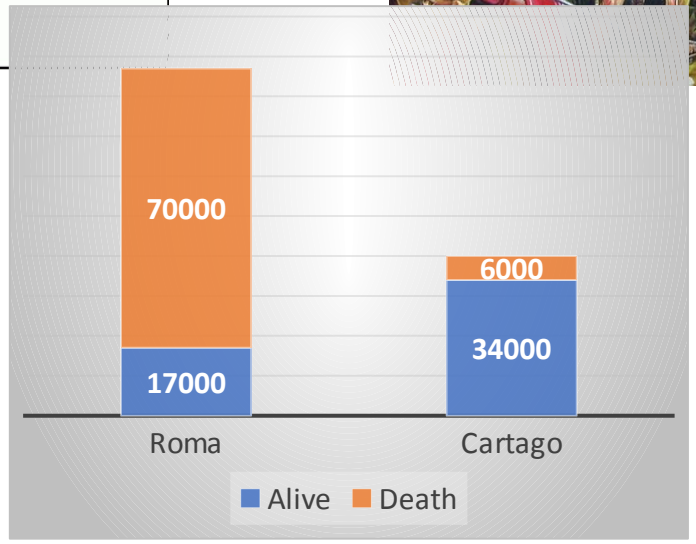


Personal communication

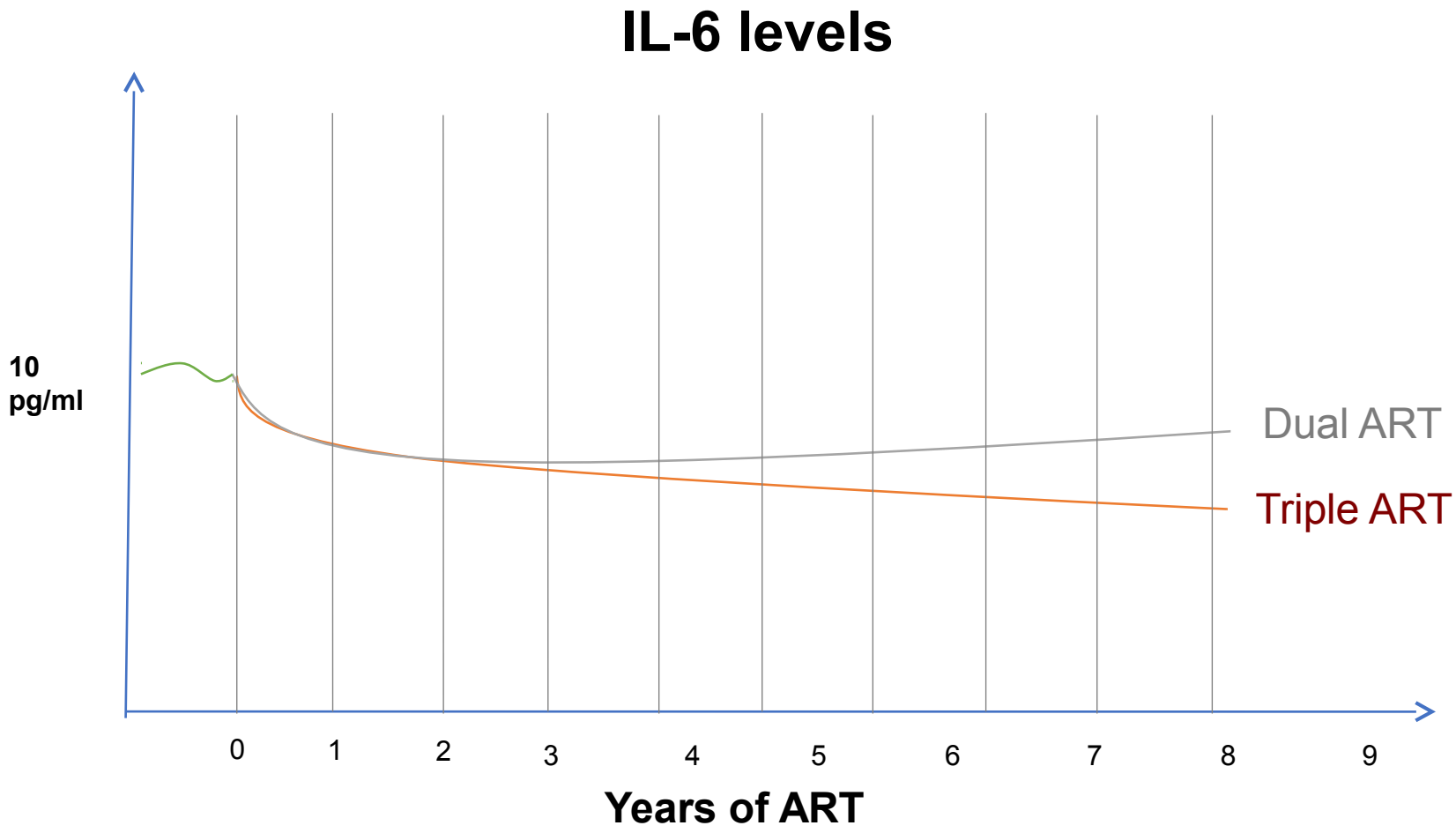
Cannae Battle

August 2nd, 216 a.C.





Barriers for the Comparison of Inflammatory Markers Dynamics Between Strategies



Sergio Serrano. Personal communication (Based on Wada. AIDS 2015)

A Plethora of Uncontrolled and Unpowered Studies to Correlate ART with Inflammatory Markers

Table 2 Safety parameters, anthropometric measurements, dual-energy X-ray absorptiometry (DXA) scan values and inflammatory markers at baseline and week 24

N=8

	Baseline	Week 24	Mean change between baseline and week 24 (95% CI)	*P*-value
Immunological measurement				
CD4 count (cells/μL) [mean (± SD, median)]	800 (± 380, 743)	842 (± 349, 974)	28 (−100, +157)	0.6
Anthropometric and fat distribution measurements				
Weight (kg) [mean (± SD, median)]	79.2 (± 14.3, 84.7)	85.3 (± 15.4, 87.5)	4.1 (+1.4, +6.9)	0.01
BMI (kg/m^2) [mean (± SD, median)]	27.1 (± 4.6, 26.8)	28.5 (± 4.9, 28.3)	1.1 (+0.1, +2.0)	0.03
Waist/hip ratio [mean (± SD, median)]	0.95 (± 0.09, 0.94)	0.95 (± 0.07, 0.97)	−0.01 (−0.09, +0.07)	0.8
Visceral adipose tissue (cm^2) [mean (± SD, median)]	129.2 (± 76.4, 102.5)	124.1 (± 50.7, 115.5)	−15.7 (−61.9, +30.4)	0.4
Subcutaneous adipose tissue (cm^2) [mean (± SD, median)]	223.4 (± 102.4, 223.4)	277.6 (± 117.4, 243.6)	32.2 (−13.1, +77.4)	0.1
Bone density measurements				
L1-L4 T-score [mean (± SD, median)]	−0.75 (± 0.98, −0.45)	−1.07 (± 1.04, −1.3)	−0.13 (−0.50, +0.24)	0.4
MCP1/CCL2 (pg/mL) [mean (± SD, median)]	267.4 (± 86.0, 265.0)	242.0 (± 68.1, 273.4)	−20.7 (−78.2, +36.9)	0.4
Insulin (UI/L) [mean (± SD, median)]	11.7 (± 6.6, 10.5)	62.4 (± 129.3, 15.3)	49.5 (−65.7, +164.7)	0.3
D-dimers (μg/L) [mean (± SD, median)]	337.8 (± 296.1, 259.5)	455 (± 477.2, 232)	110.4 (−103.9, +324.8)	0.2

ALAT, alanine transaminase; BMI, bone mineral index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; SD, standard deviation; TNF, tumour necrosis factor; MCP1/CCL2, monocyte chemoattractant protein 1.

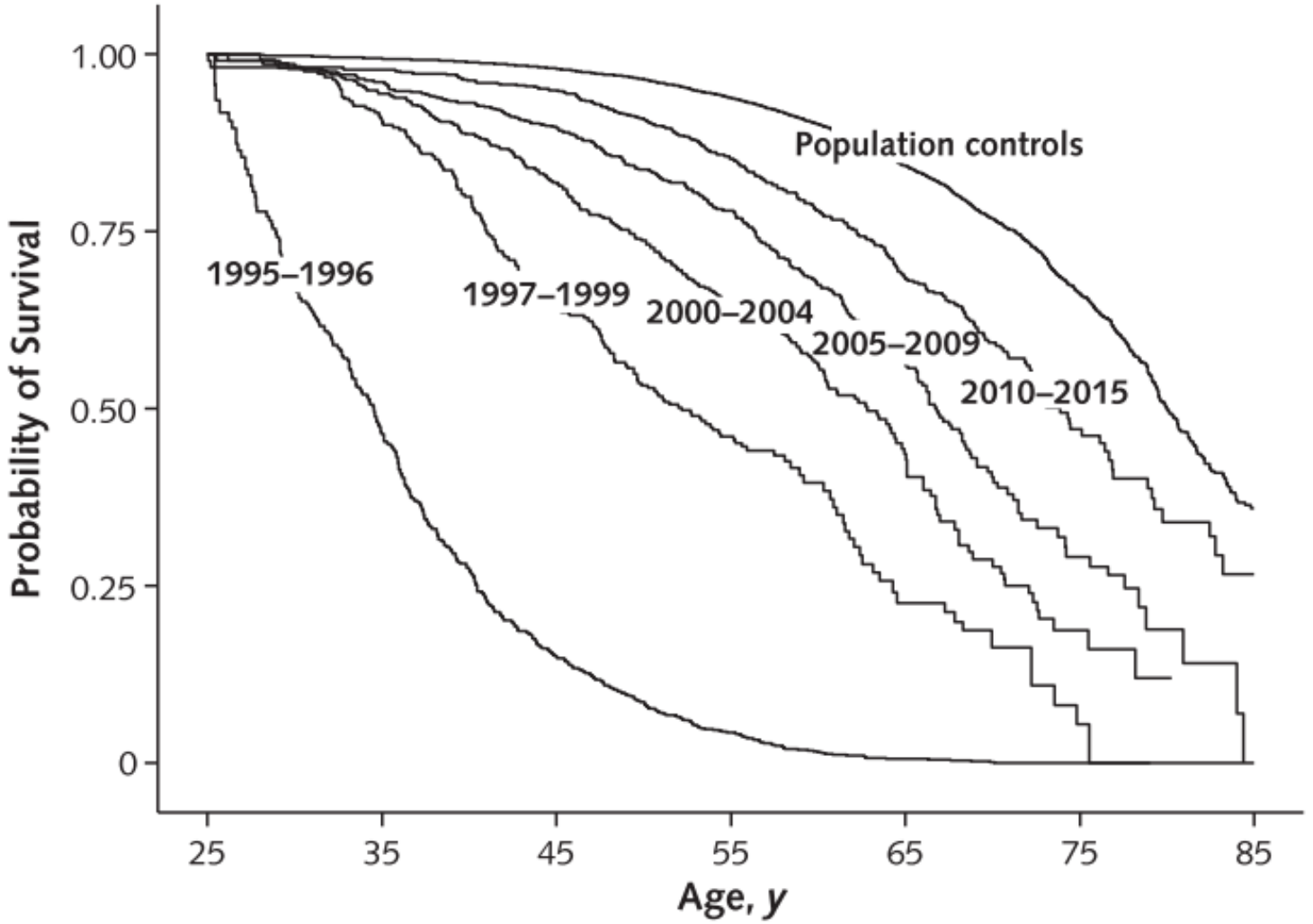
"HIV-1 RNA remained undetectable in all samples of blood, cerebrospinal fluid and sperm throughout the 24 weeks, except for one cerebrospinal fluid sample with a value of 28 HIV-1 RNA copies/mL at week 24"

"CONCLUSIONS: HIV-1 reservoirs were well controlled on DTG monotherapy over a period of 24 weeks"

Sculier. HIV Medicine 2018

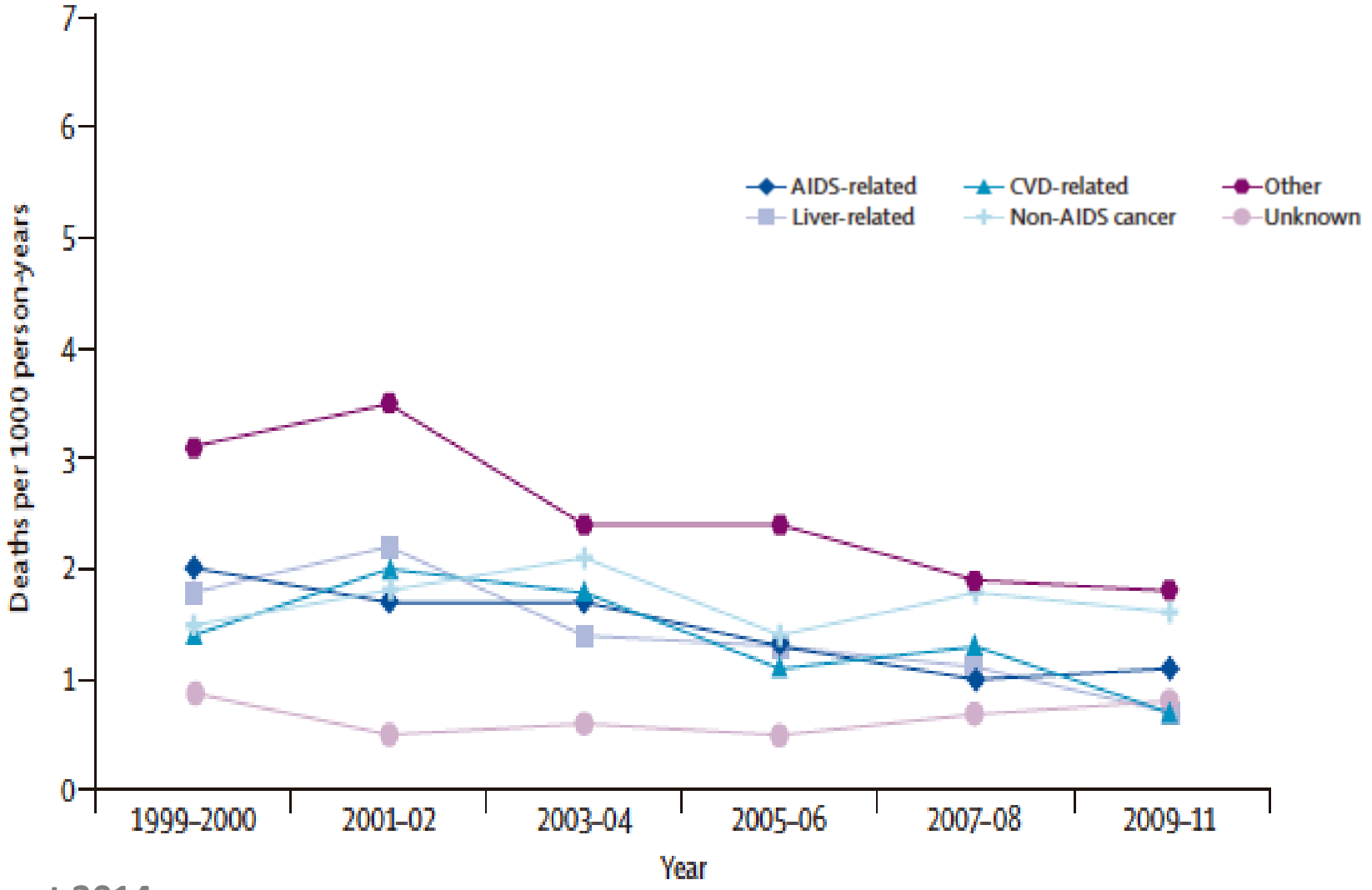
Where do we stand after 22 years of triple ART?

Higher survival in HIV-infected persons since the introduction of HAART (3DR)



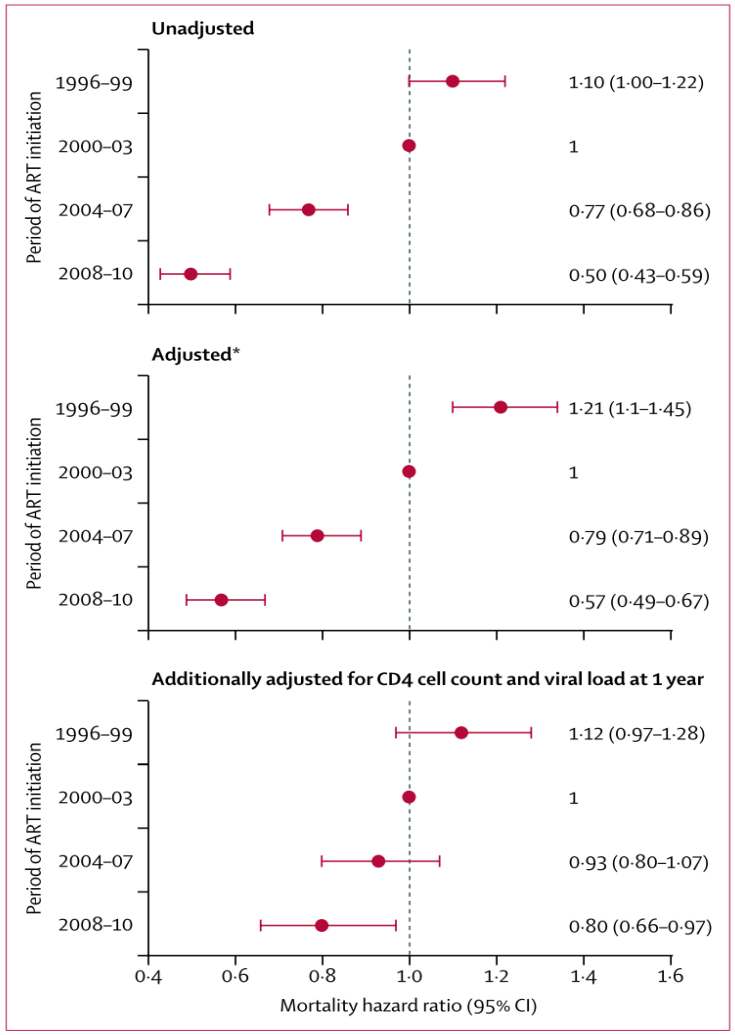
Lohse & Obels. Annals Intern Med 2016

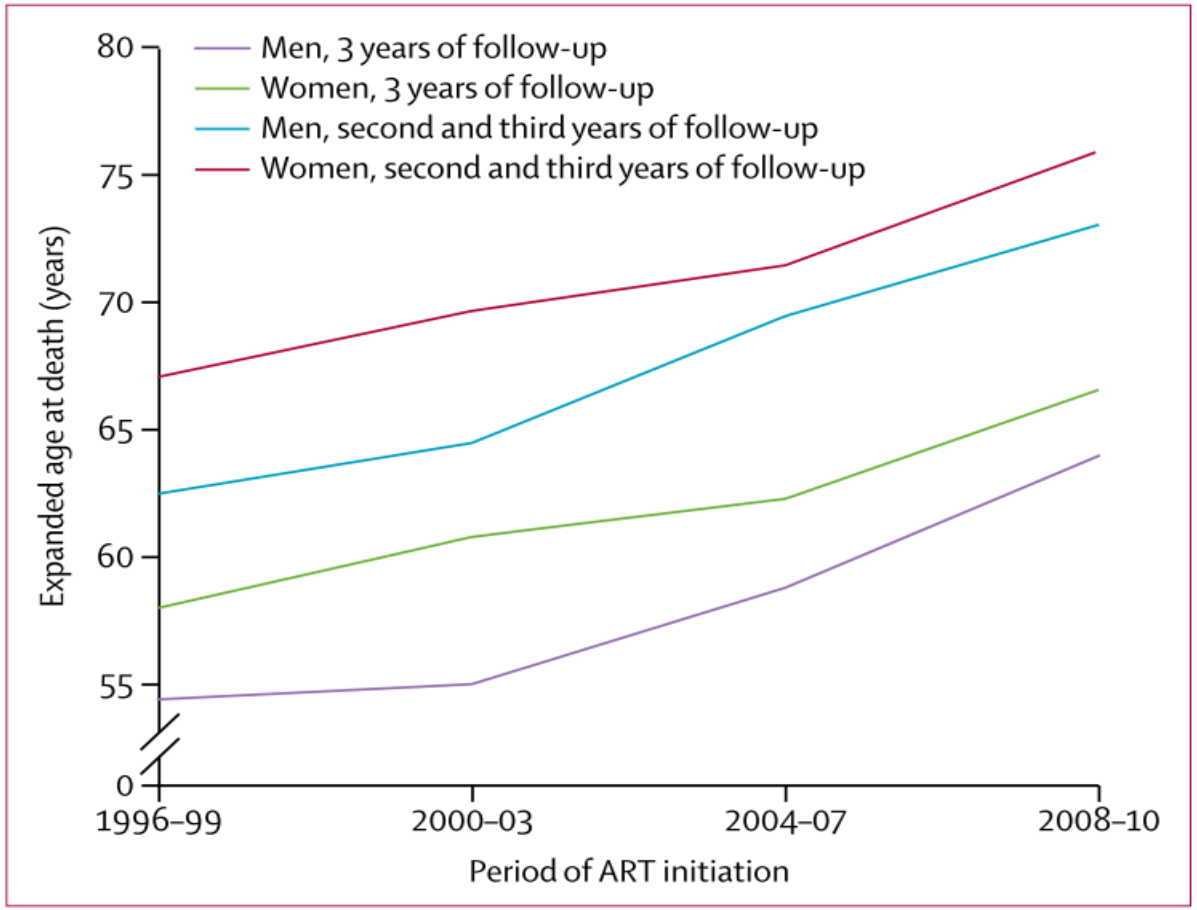
AIDS and even most non-AIDS events (CAD, liver) have slowly declined, even during the late ART era



Smith C et al. Lancet 2014

Survival During the First 3 years of ART Continues to Improve

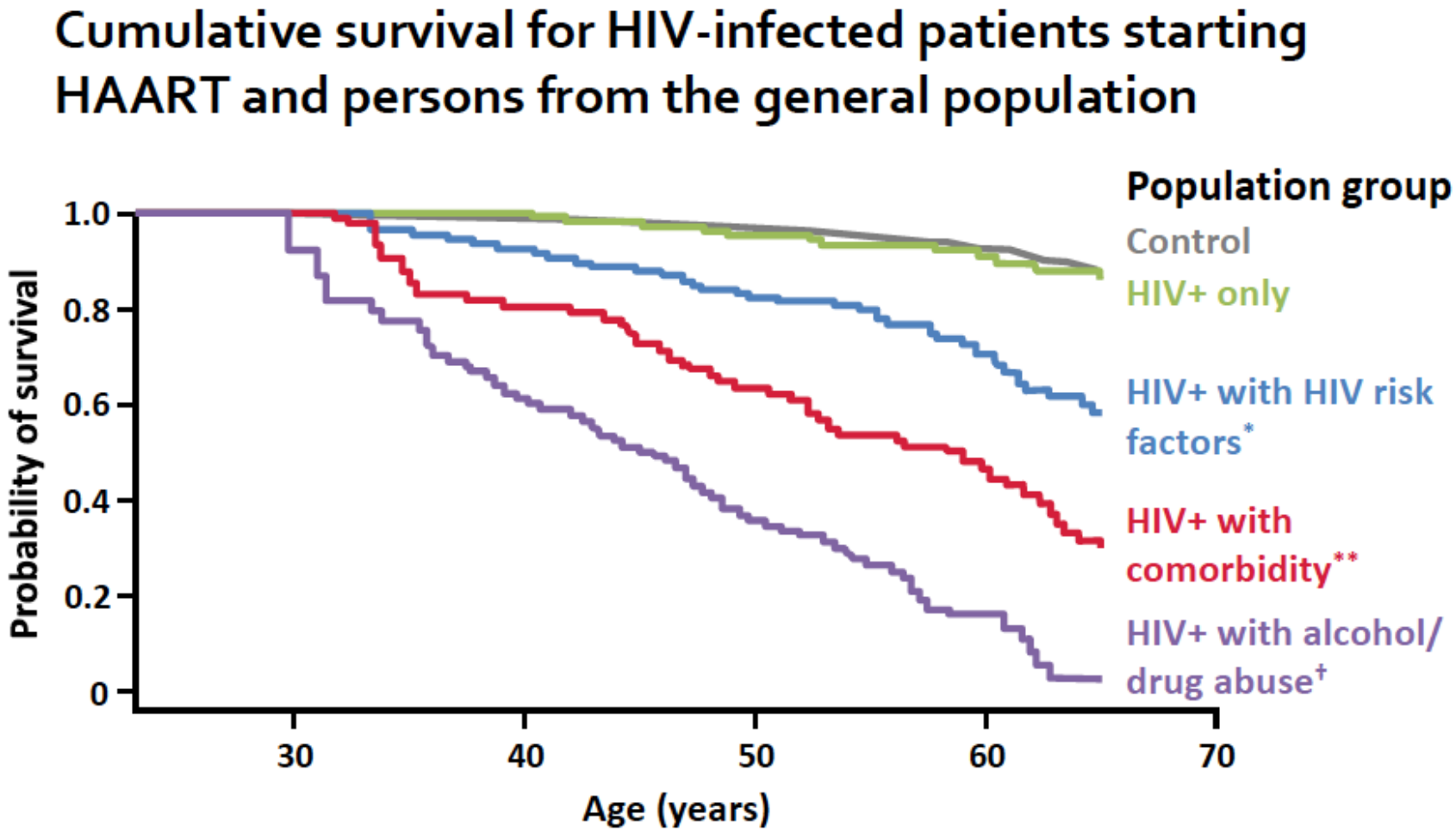




"Even in the late ART era, survival during the first 3 years of ART continues to improve, which probably reflects transition to less toxic antiretroviral drugs, improved adherence, prophylactic measures, and management of comorbidity".

ART-CC (Trickey et al). Lancet HIV 2017

Normal Life Expectancy in People Living with HIV when Controlling for Risk Factors



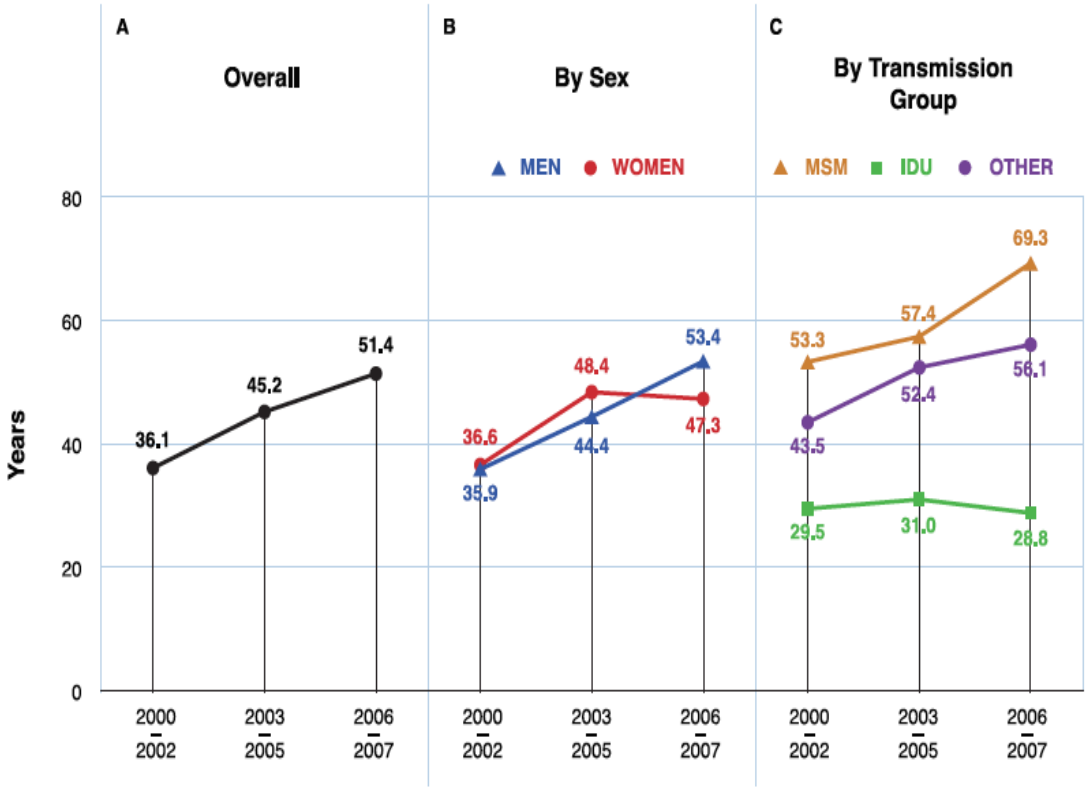
* Viral load >49 copies/mL, CD4 <200 cells/μL, AIDS-defining disease **as defined in the Charlson comorbidity index (CCI);
† Drug abuse reported as route of HIV transmission

Obel. Plos One 2011

Obel N *et al.* PLoS ONE 2011;6(7):e22698

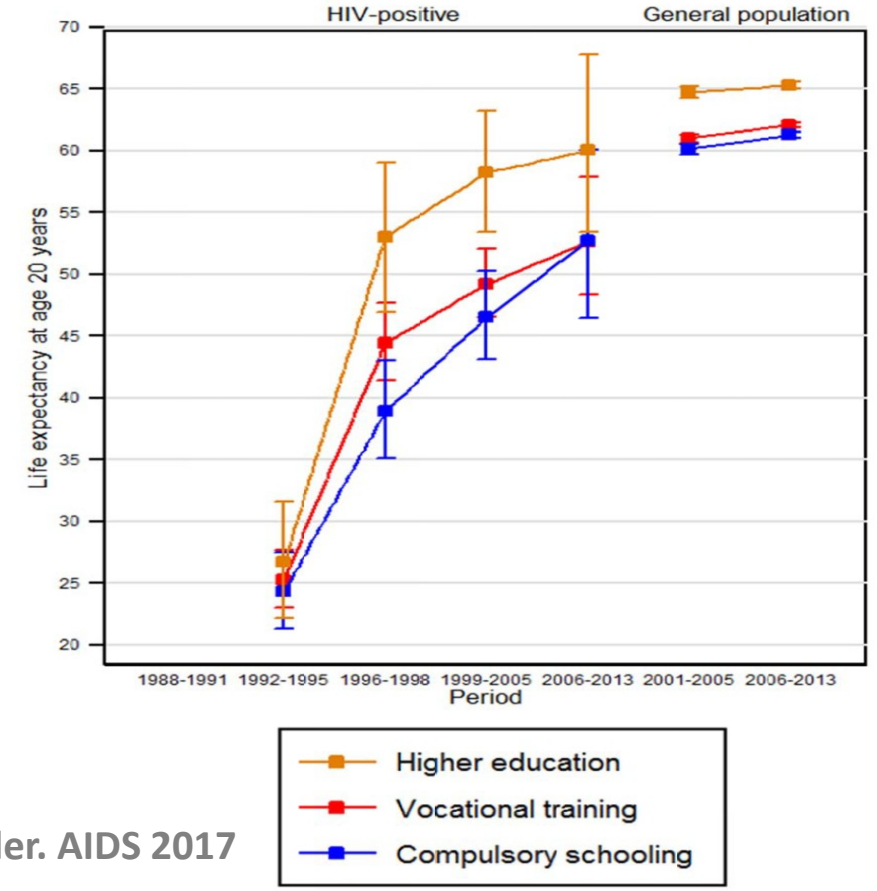
Life-Expectancy Could be Already Comparable to the General Population

NA-ACCORD: Mid-point life expectancy estimates at age 20 years



Samji H. PLOS ONE. 2013

Normal life-expectancy in higher educational level in HIV-infected subjects



Gueler. AIDS 2017

Hay dúos… y dúos

Y hay tríos… y tríos

Conclusions

Monotherapy

Inferior

- Higher rates of virologic failure.
- Important proof of concept showing the risks of decreasing the number of drugs/nukes-free therapies.

Dual therapy

Promising, but still lots of unknowns

- Non-inferior for VL suppression in switching and ART initiation (one study)
- Non-inferior for AE in switching.
- Unknown long-term effects on residual replication and inflammation.
- Unknown long-term effects on prognosis

Triple therapy

Still standard

- Has allowed to nearly life expectancy.
- Need to compare the differences on surrogate markers of non-AIDS events with dual therapy.

¡Gracias!

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Twitter: @serranovillar

Monument Valley, Utah