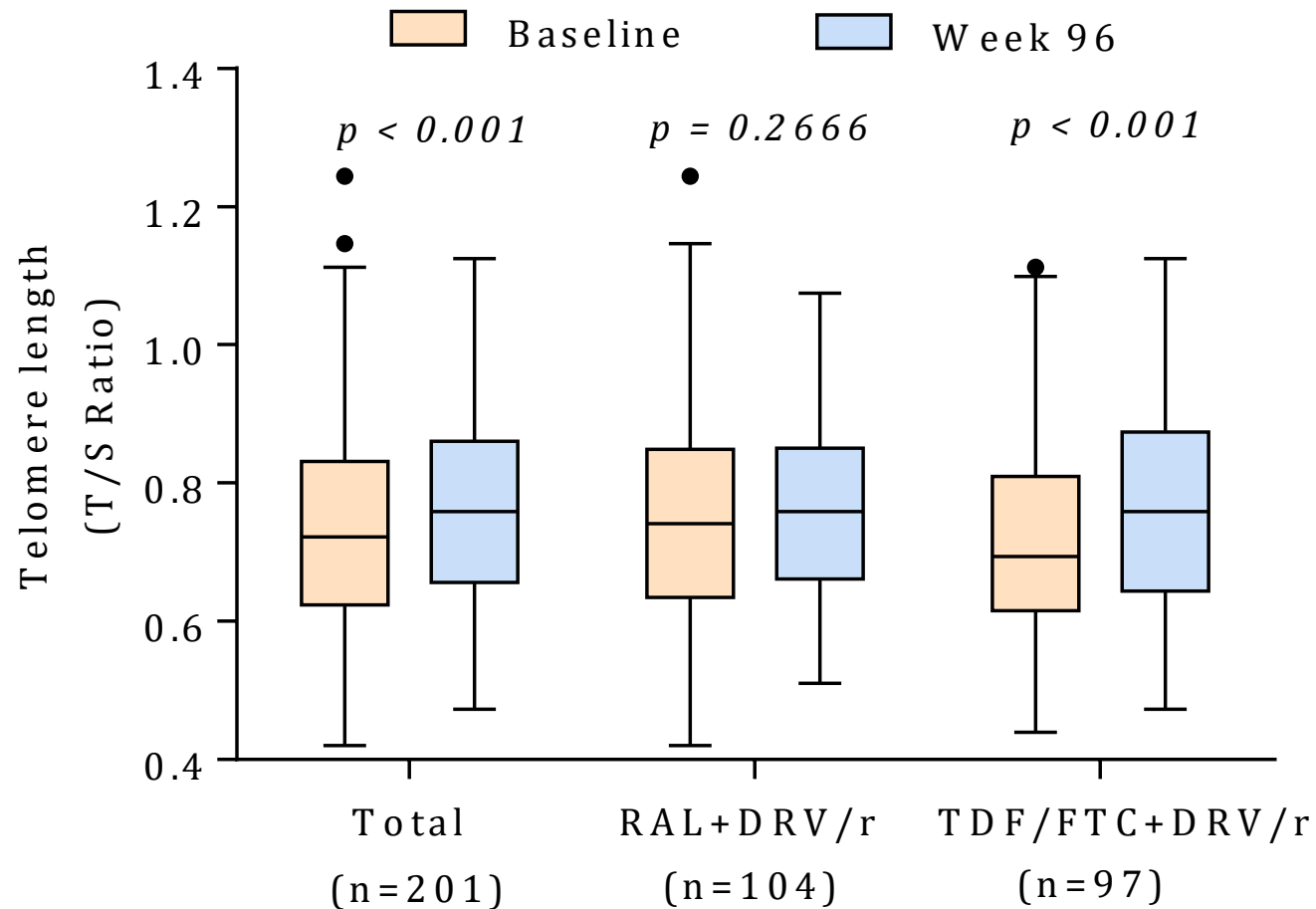


Telomere Length Change



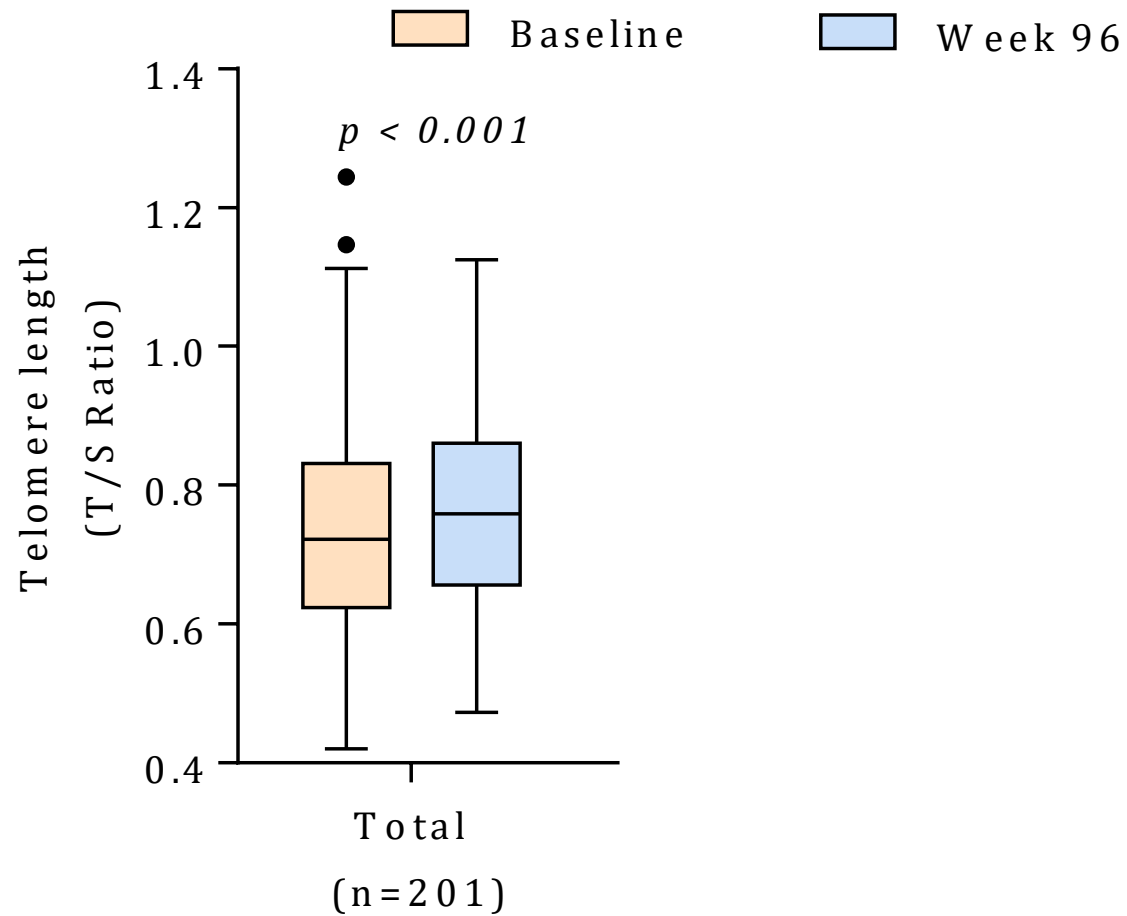
RAL: Raltegravir. DRV/r: Darunavir/ritonavir. TDF: Tenofovir Disoproxil Fumarate.
FTC: Emtricitabine.

“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, $p=0.038$)”

Participant characteristics

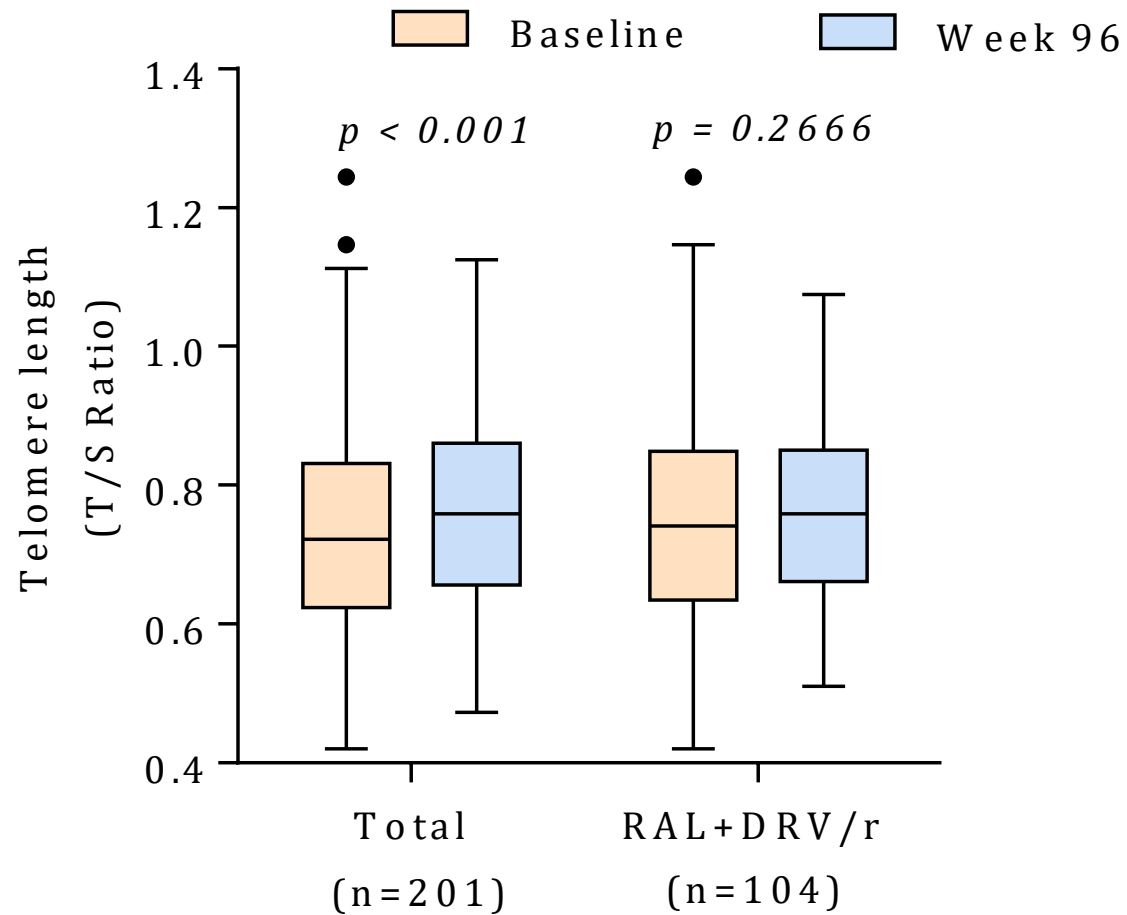
	RAL + DRV/r N=104	TDF/FTC + DRV/r N=97	p-value
Age, (yr) *	38.7 (10.4)	38.6 (10.8)	0.961
Female, n(%)	11 (10.6)	11 (11.3)	0.862
Smoking (Currently), n(%)	35 (33.7)	39 (40.2)	0.417
Alcohol use (Currently), n(%)	4 (3.8)	10 (10.3)	0.197
Time since HIV diagnosis (yr) *	2.2 (3.3)	2.0 (2.8)	0.699
Baseline 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

Telomere Length Change



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

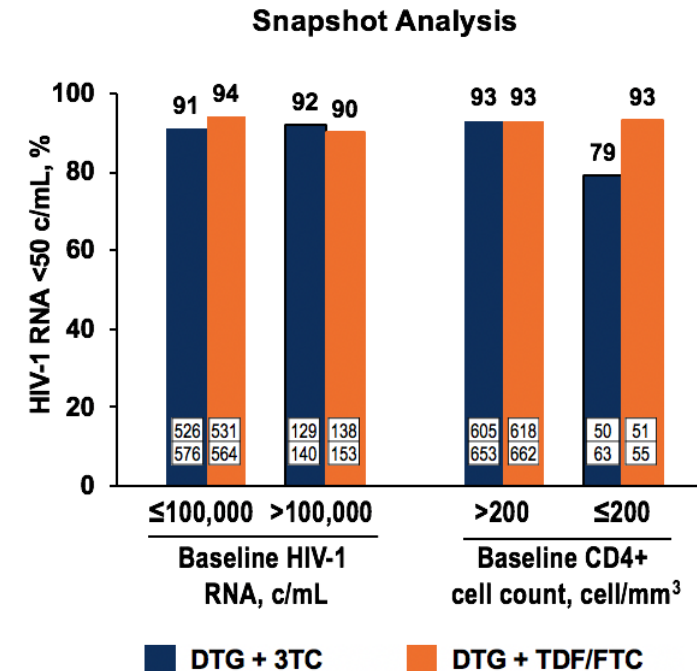
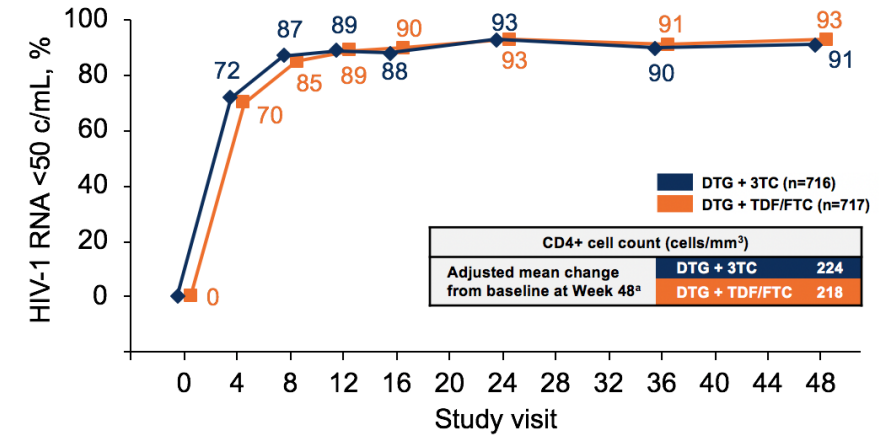
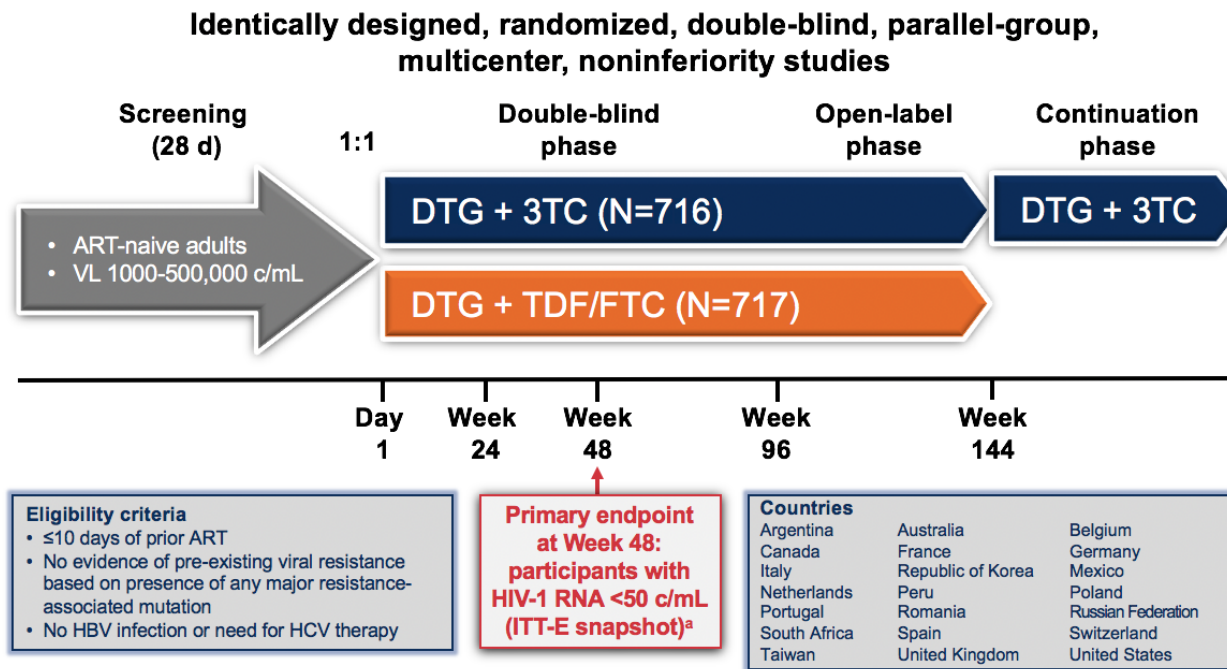
Telomere Length Change



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

GEMINI 1-2

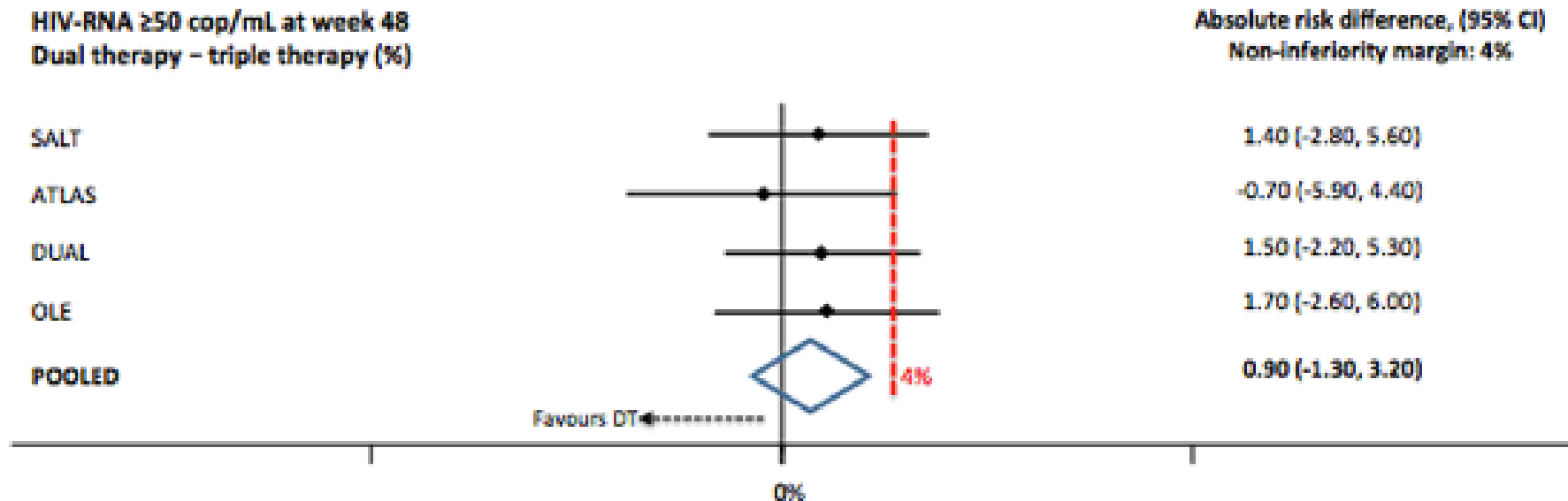
DTG+3TC vs. DTG+TDF/FTC



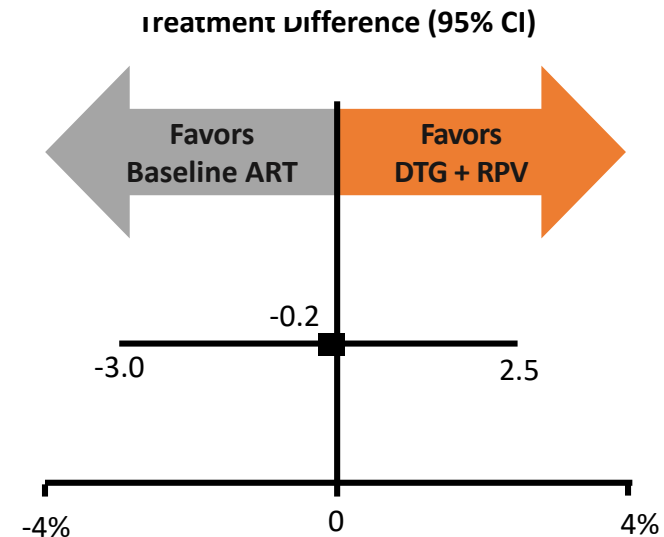
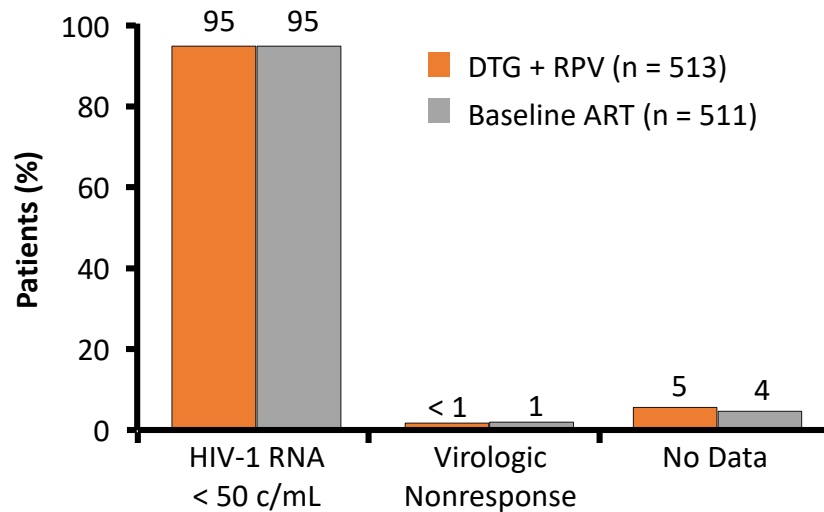
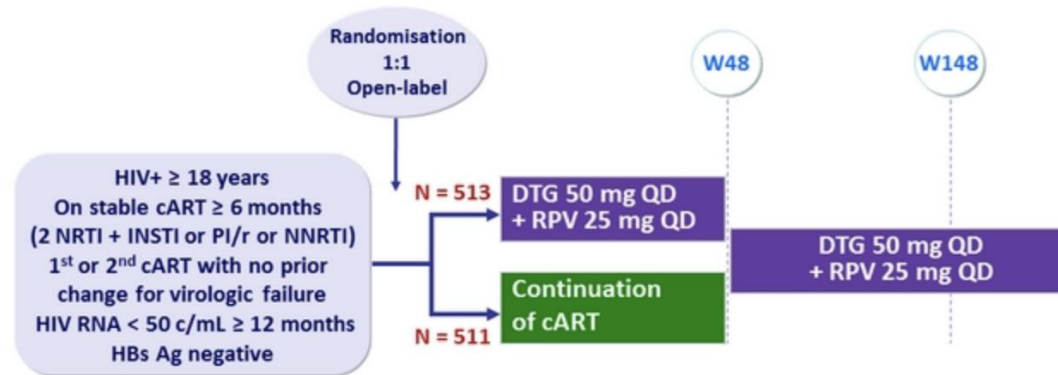
Individual Patient-Data Metanalysis of Dual Therapy RCT

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%)

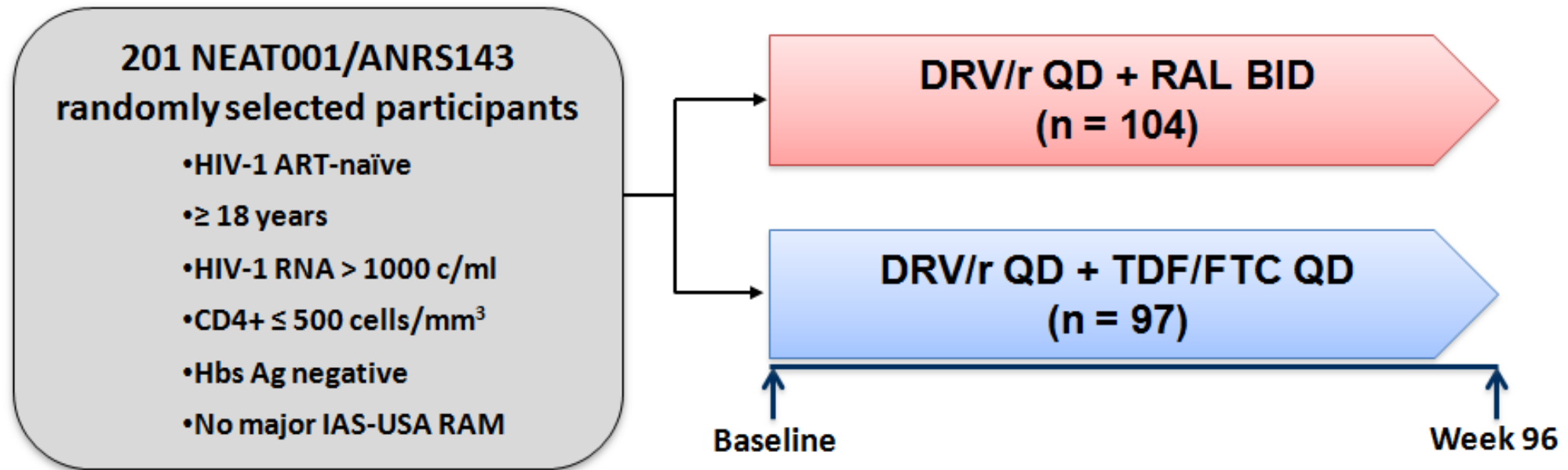


SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV in Patients With No Previous VF



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).



SWORD Studies: Inflammation (Week 48)

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

Biomarker	DTG + RPV		CAR		Week 48 difference, DTG+RPV – CAR (95% CI)
	n	Mean (median [range])	n	Mean (median [range])	
Inflammation					
C-RP, mg/L					
Baseline*	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*	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*	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*	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*	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*	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*	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. *Baseline values are actual values.

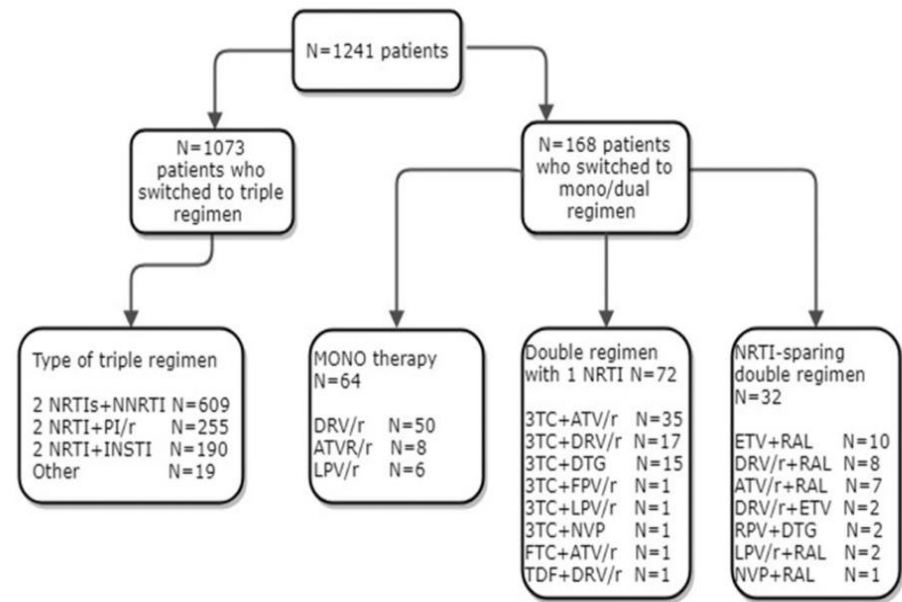
“No consistent pattern of change from baseline to week 48 or differentiation between the dolutegravir-rilpivirine group and the CAR group was observed for the inflammatory or cardiovascular biomarkers: interleukin-6, C-reactive protein, soluble vascular cell adhesion molecule-1, soluble CD14, soluble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

Llibre. Lancet Infect Dis 2017



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

Cristina Mussini^{1*}, Patrizia Lorenzini², Alessandro Cozzi-Lepri³, Giulia Marchetti⁴, Stefano Rusconi⁴, Andrea Gori⁴, Silvia Nozza⁵, Miriam Lichtner⁶, Andrea Antinori², Andrea Cossarizza⁷, Antonella d’Arminio Monforte⁴ 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?**

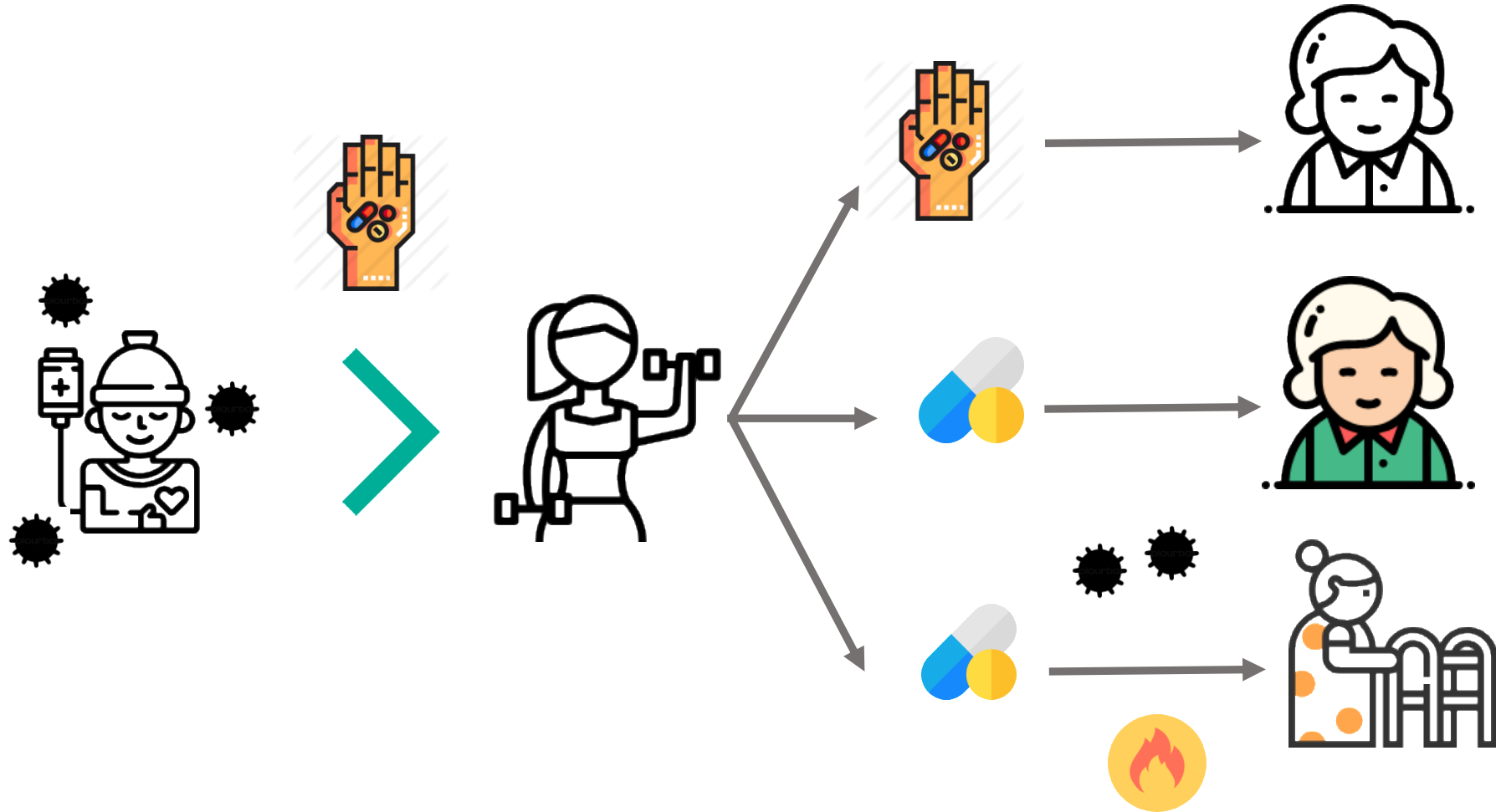
Current Nukes

- 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, pregnancy, HBV,...)
- Have no significant interactions
- Have a favorable safety profile
- In triple ART protect against the development of mutations



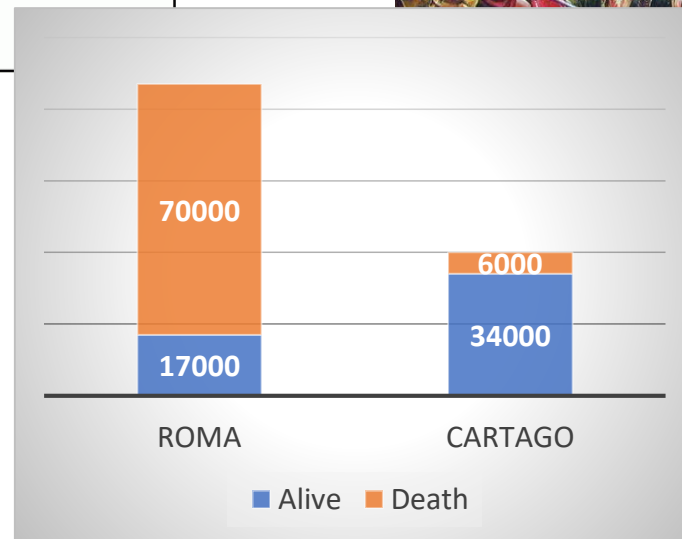
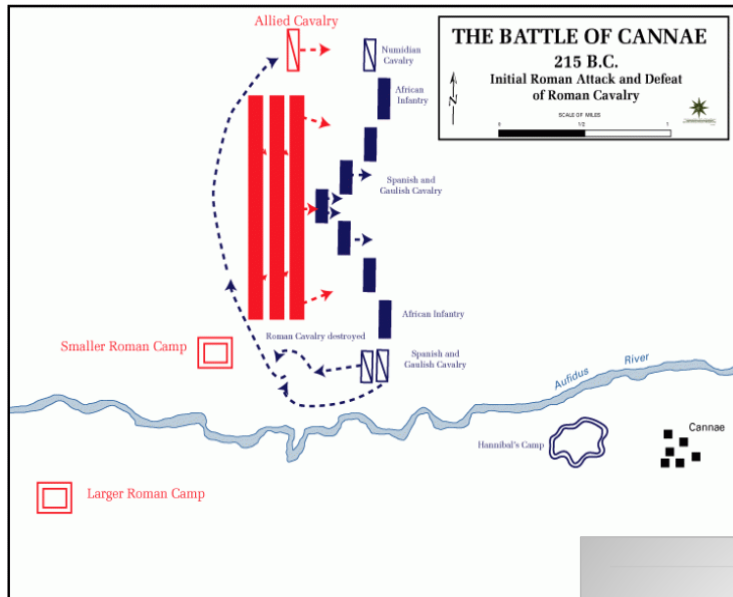
"It pains me to tell you this, but it ain't broke."

Rationale for dual therapy benefits and risks

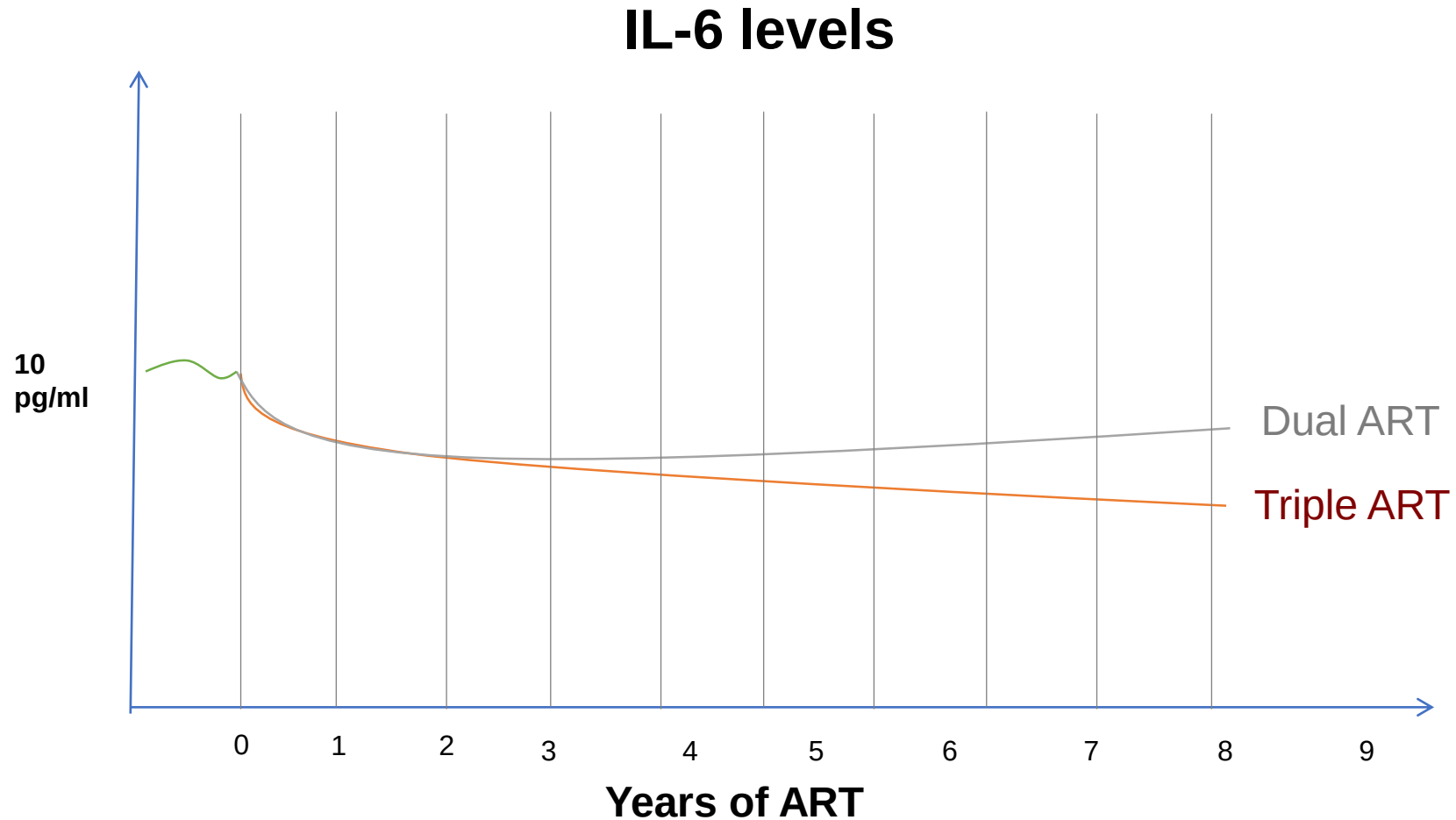


Cannae Battle

August 2nd, 216 a.C.



Barriers for the Comparison of Inflammatory Markers Dynamics Between Strategies



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

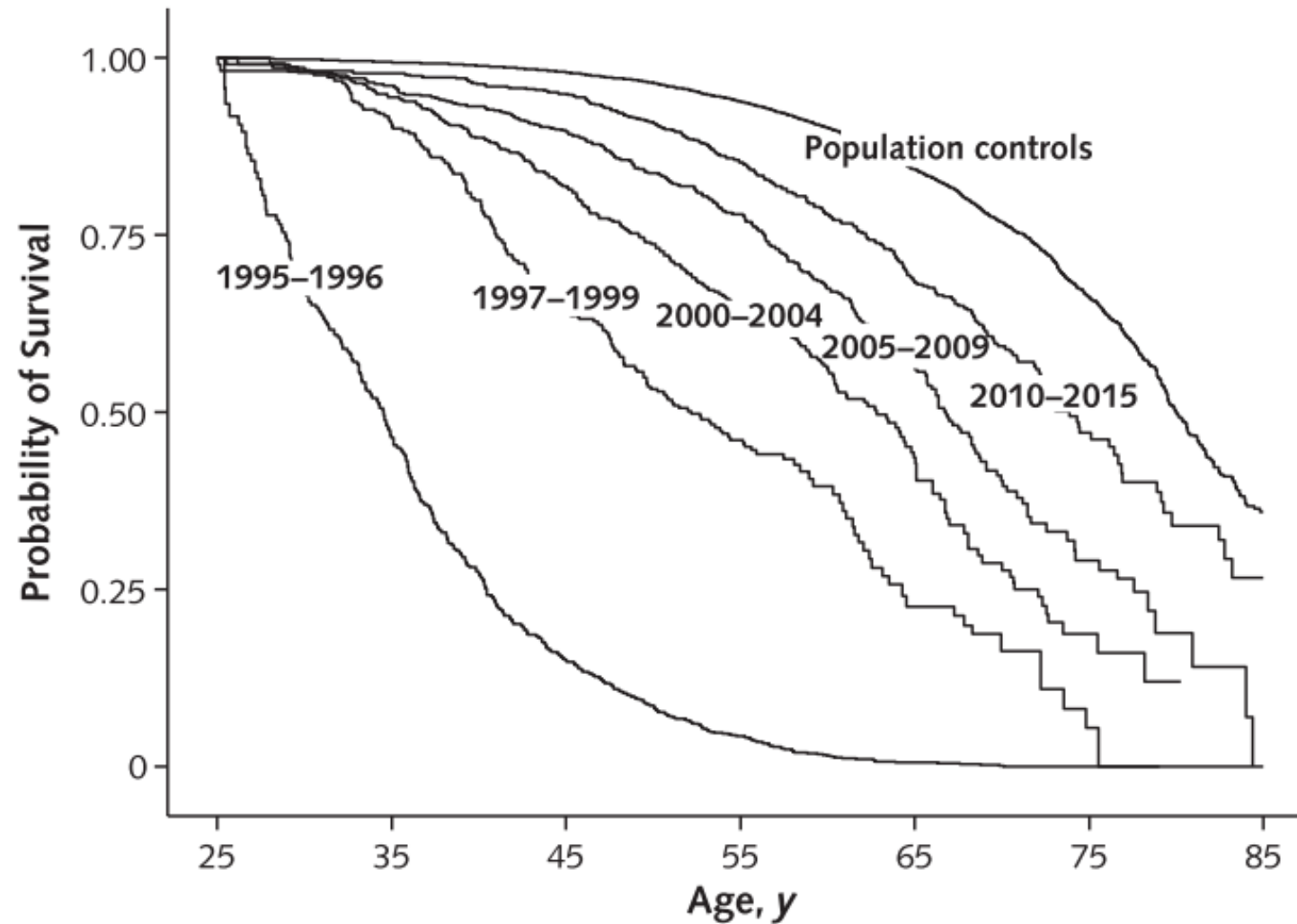
Table 2 Safety parameters, anthropometric measurements, dual-energy X-ray absorptiometry (DXA) scan values and inflammatory markers at baseline and week 24

N=8	Baseline	Week 24	Mean change between baseline and week 24 (95% CI)	P-value
Immunological measurement				
CD4 count (cells/ μ L) [mean ($\pm$ SD, median)]	800 ($\pm$ 380, 743)	842 ($\pm$ 349, 974)	28 (−100, +157)	0.6
<i>“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”</i>				
Anthropometric and fat distribution measurements				
Weight (kg) [mean ($\pm$ SD, median)]	79.2 ($\pm$ 14.3, 84.7)	85.3 ($\pm$ 15.4, 87.5)	4.1 (+1.4, +6.9)	0.01
BMI (kg/m^2) [mean ($\pm$ SD, median)]	27.1 ($\pm$ 4.6, 26.8)	28.5 ($\pm$ 4.9, 28.3)	1.1 (+0.1, +2.0)	0.03
Waist/hip ratio [mean ($\pm$ SD, median)]	0.95 ($\pm$ 0.09, 0.94)	0.95 ($\pm$ 0.07, 0.97)	−0.01 (−0.09, +0.07)	0.8
Visceral adipose tissue (cm^2) [mean ($\pm$ SD, median)]	129.2 ($\pm$ 76.4, 102.5)	124.1 ($\pm$ 50.7, 115.5)	−15.7 (−61.9, +30.4)	0.4
Subcutaneous adipose tissue (cm^2) [mean ($\pm$ SD, median)]	223.4 ($\pm$ 102.4, 223.4)	277.6 ($\pm$ 117.4, 243.6)	32.2 (−13.1, +77.4)	0.1
Bone density measurements				
L1–L4 T-score [mean ($\pm$ SD, median)]	−0.75 ($\pm$ 0.98, −0.45)	−1.07 ($\pm$ 1.04, −1.3)	−0.13 (−0.50, +0.24)	0.4
<i>“CONCLUSIONS: HIV-1 reservoirs were well controlled on DTG monotherapy over a period of 24 weeks”</i>				
MCP1/CCL2 (pg/mL) [mean ($\pm$ SD, median)]	267.4 ($\pm$ 86.0, 265.0)	242.0 ($\pm$ 68.1, 273.4)	−20.7 (−78.2, +36.9)	0.4
Insulin (UI/L) [mean ($\pm$ SD, median)]	11.7 ($\pm$ 6.6, 10.5)	62.4 ($\pm$ 129.3, 15.3)	49.5 (−65.7, +164.7)	0.3
D-dimers ($\mu\text{g}/\text{L}$) [mean ($\pm$ SD, median)]	337.8 ($\pm$ 296.1, 259.5)	455 ($\pm$ 477.2, 232)	110.4 (−103.9, +324.8)	0.2

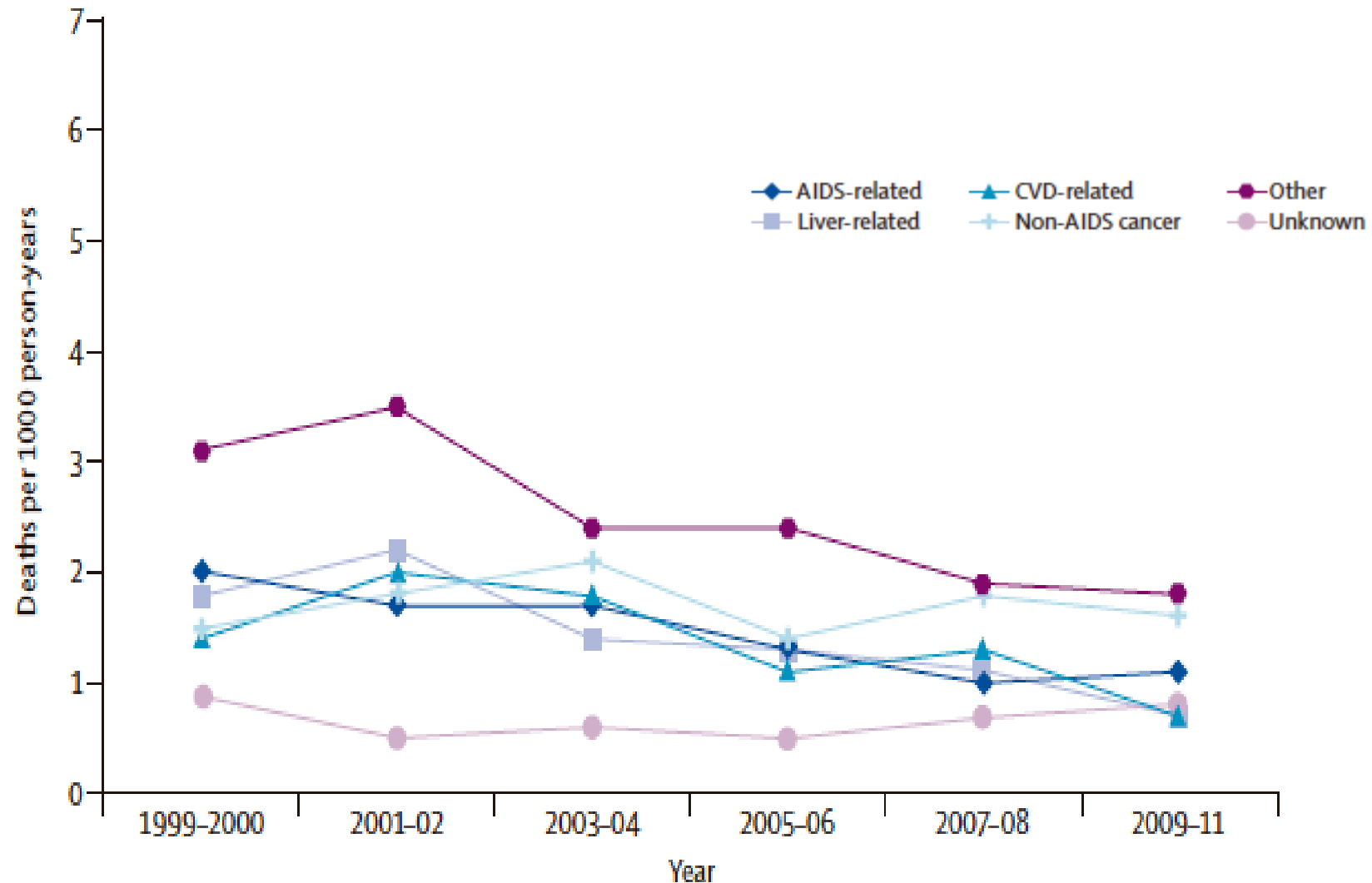
ALAT, alanine transaminase; BMI, bone mineral index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; SD, standard deviation; TNF, tumour necrosis factor; MCP1/CCL2, monocyte chemoattractant protein 1.

Where do we stand
after 22 years of
triple ART?

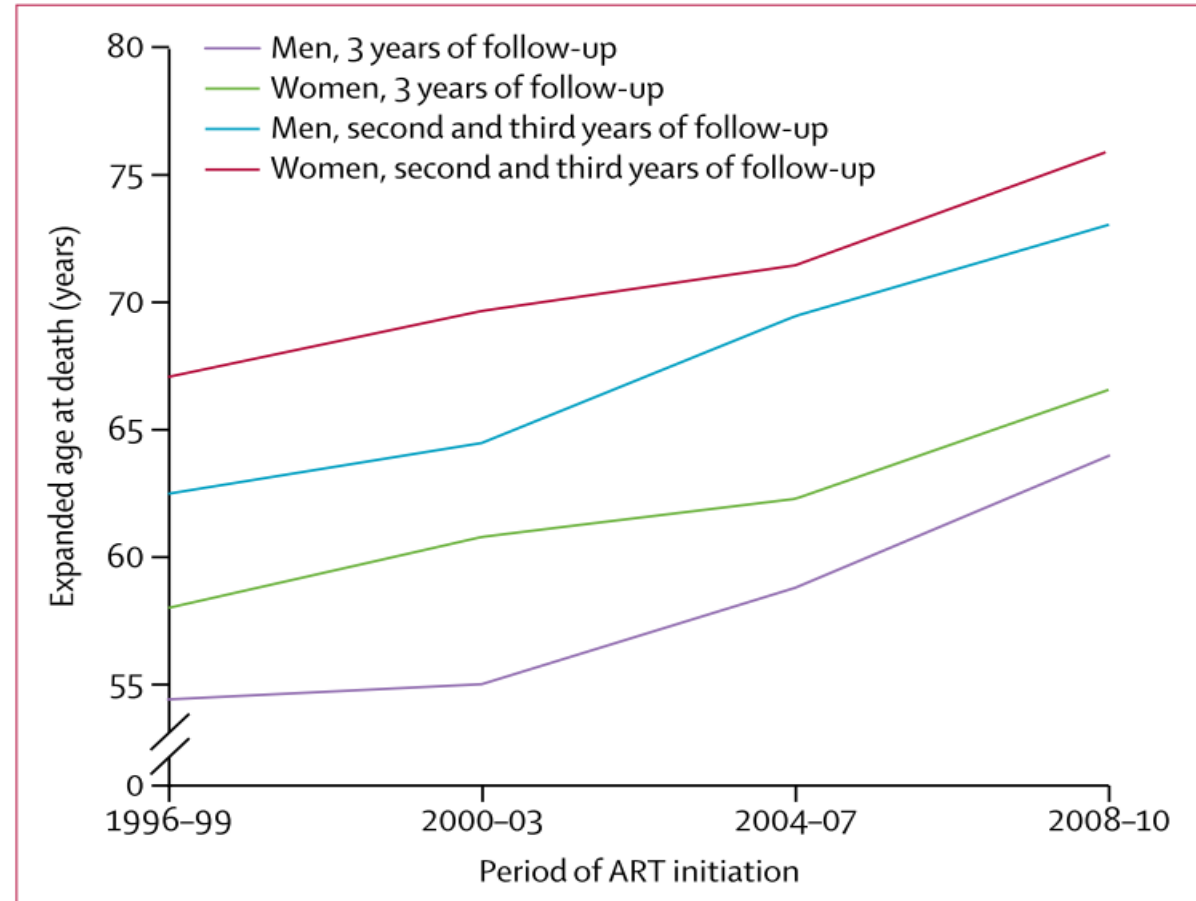
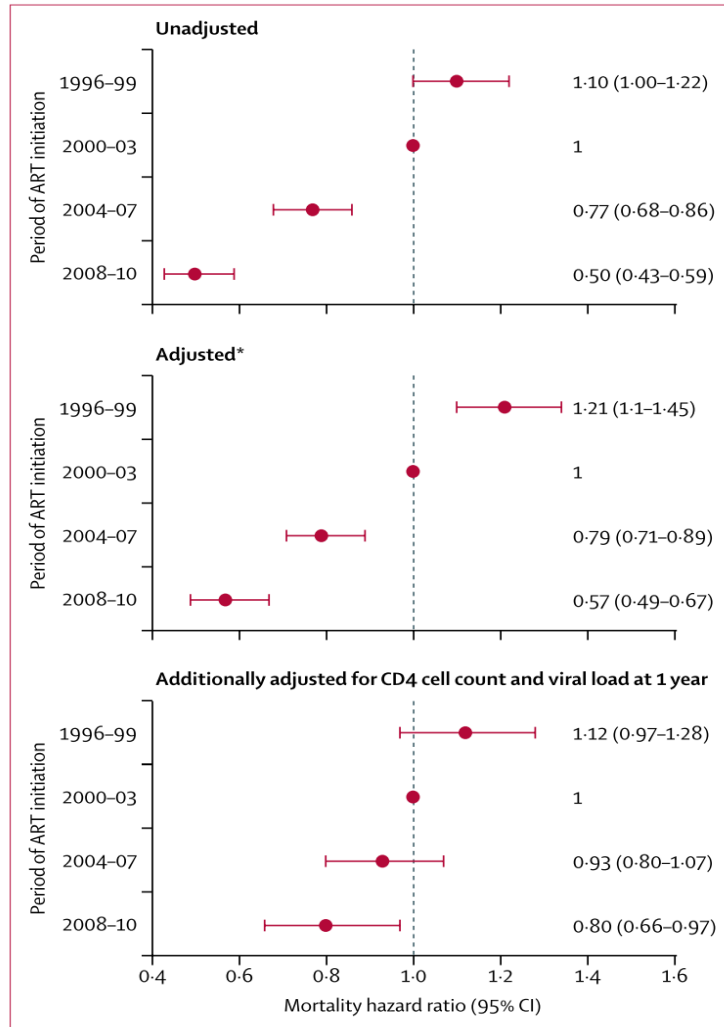
Higher survival in HIV-infected persons since the introduction of HAART (3DR)



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



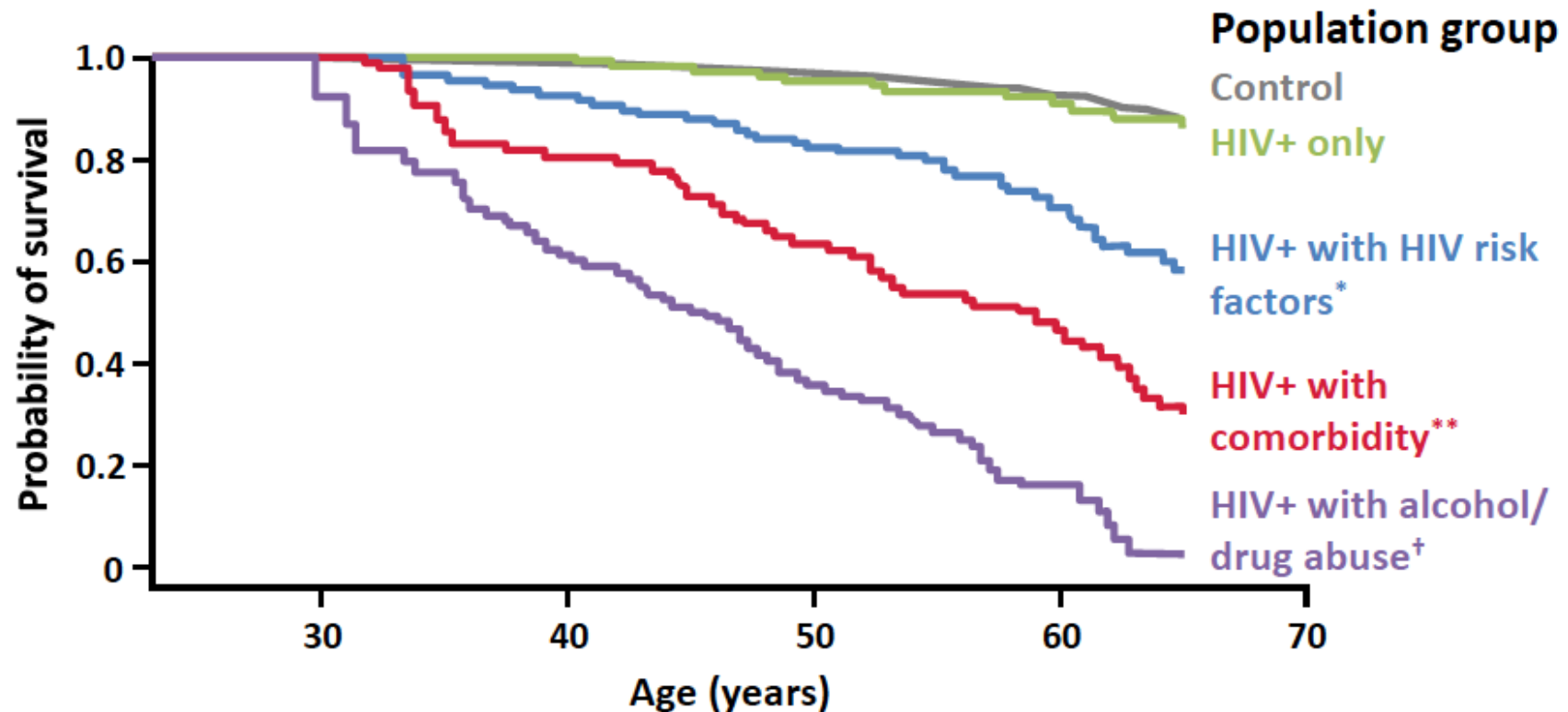
Survival During the First 3 years of ART Continues to Improve



“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”.

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

Cumulative survival for HIV-infected patients starting HAART and persons from the general population

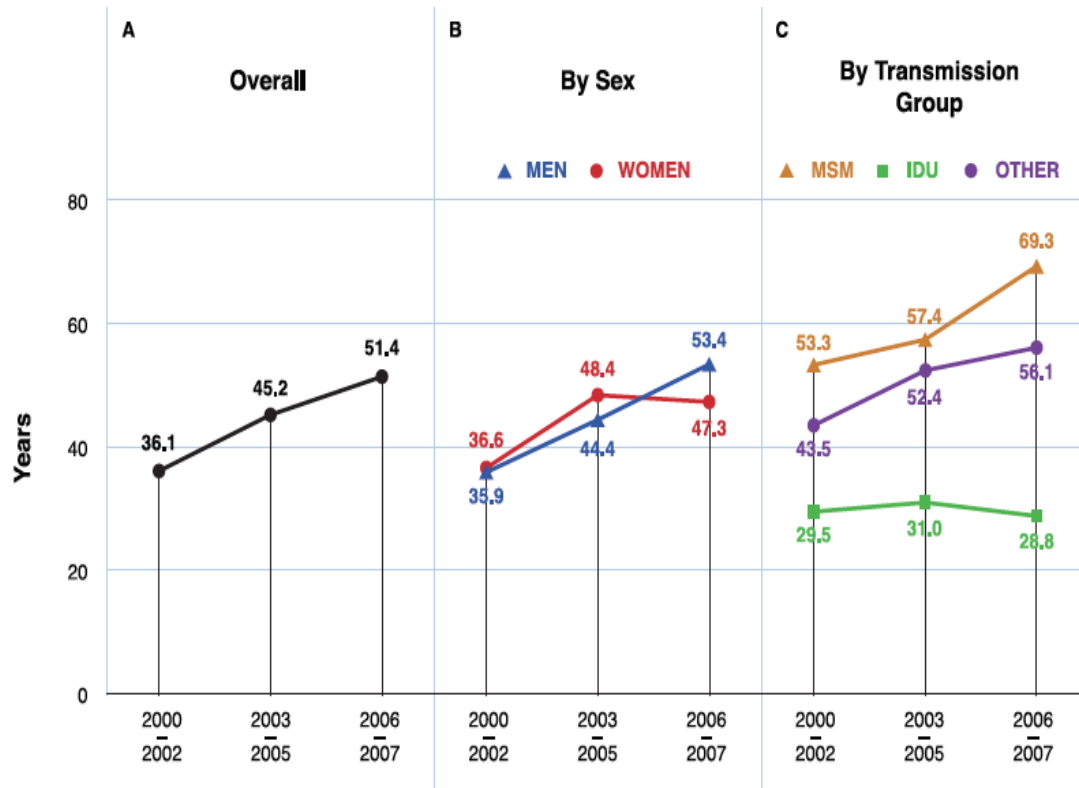


* Viral load >49 copies/mL, CD4 <200 cells/ μ L, AIDS-defining disease **as defined in the Charlson comorbidity index (CCI);

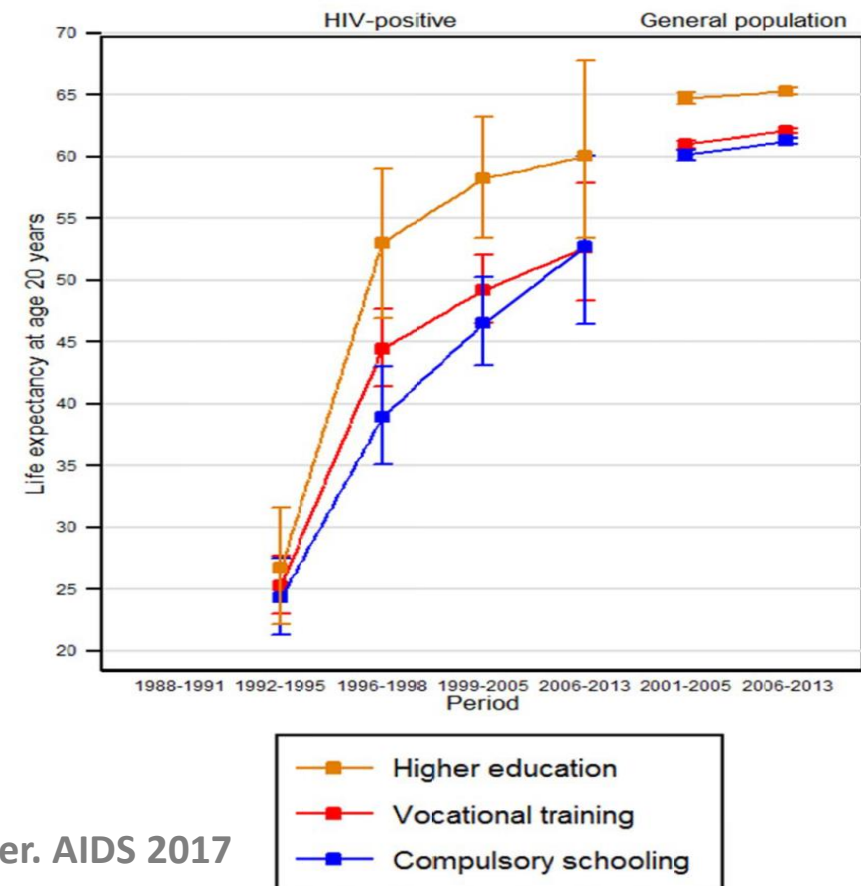
† Drug abuse reported as route of HIV transmission

Life-Expectancy Could be Already Comparable to the General Population

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



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



Hay dúos... y
dúos



Y hay tríos... y
tríos



Conclusions

Monotherapy

Inferior

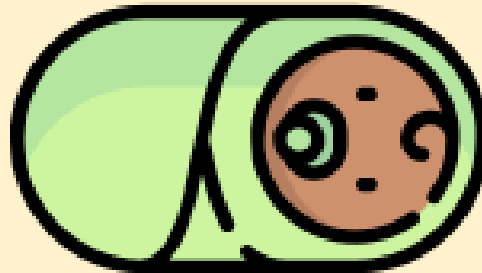
- Higher rates of virologic failure.
- Important proof of concept showing the risks of decreasing the number of drugs/nukes-free therapies.



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!

