Roma 20 settembre 2018

Regimi a due farmaci: opportunità e allerte

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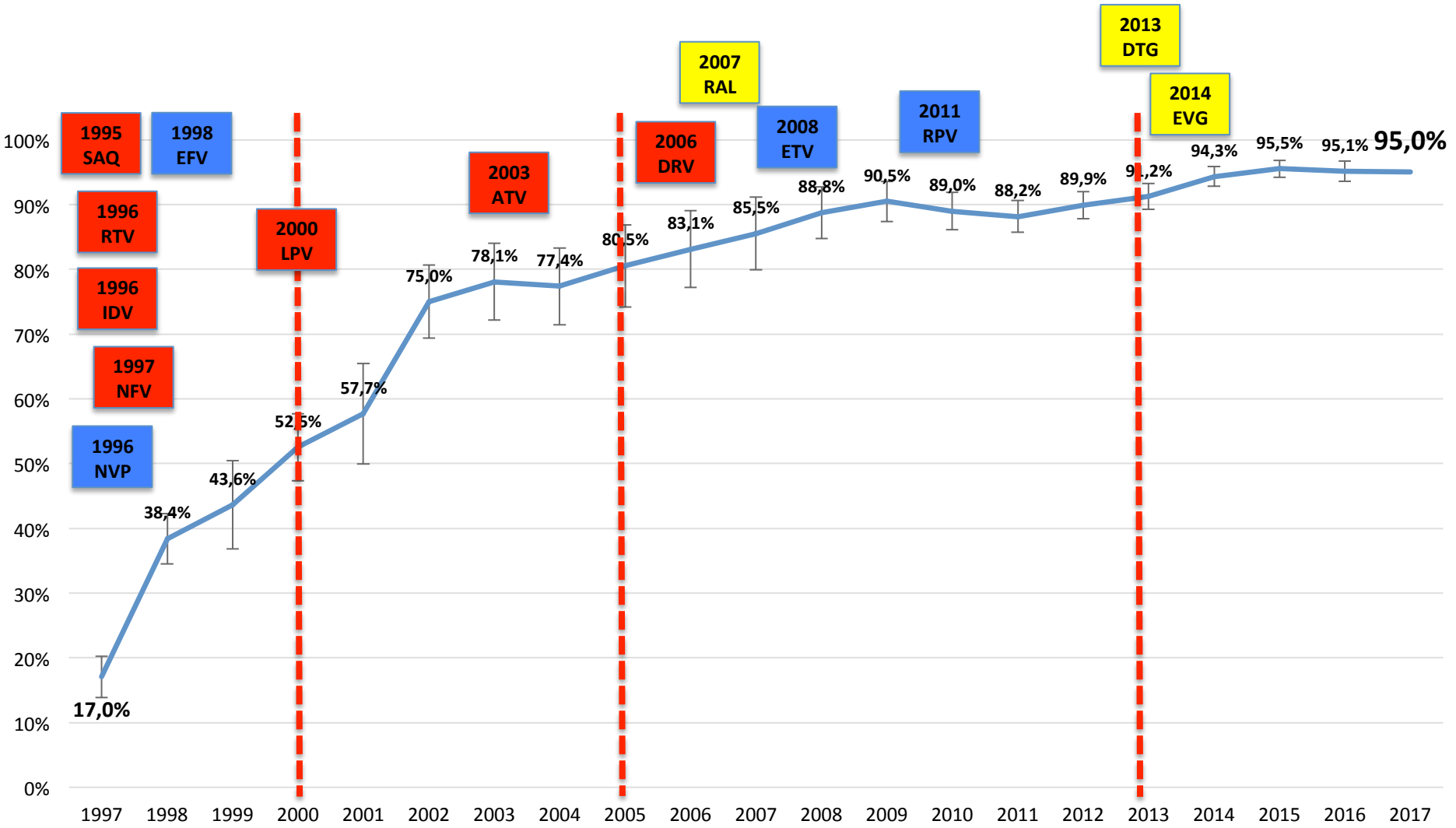
PTV
Azienda Ospedaliera Univers
POLICLINICO TOR VERGATA

Disclosures

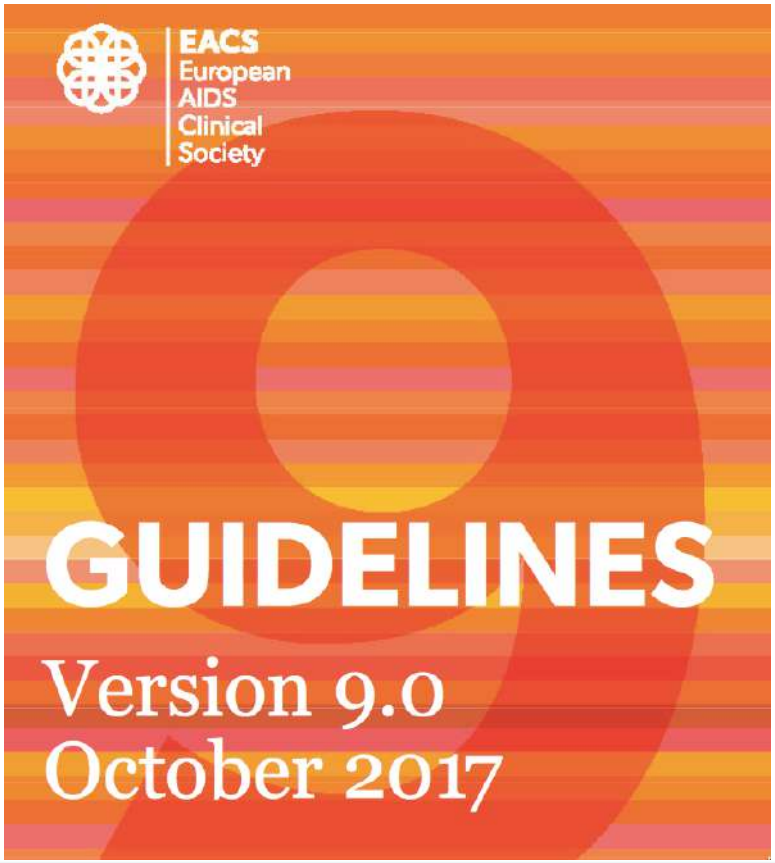
I have received funding for membership of Advisory Boards, for the preparation of educational materials, for research and educational grants, for membership of speaker panels and for support for travel to conferences from the following companies:

- Gilead Sciences
- Bristol-Myers Squibb
- Janssen-Cilag
- Viiv Healthcare
- Abbott Pharmaceuticals
- Merck Sharp and Dohme
- Abbvie
- Astra Zeneca
- Boheringer Ingelheim
- Pfizer

Proportion of patients with a VL<=80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation



Jan 2018 Report



Definition of virologically suppressed

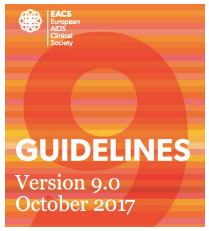
Clinical trials exploring switching strategies have defined suppression as an HIV-VL < 50 copies/mL for at least 6 months.

Principles

GUIDELINES
Version 9.0
October 2017

Clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. Just because the HIV-VL is suppressed it should not be assumed that the HIV-positive person is well adapted and tolerating the current regimen.

- ✓ In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy.
- ✓ The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures.
- ✓ A complete ARV history with HIV-VL, tolerability issues and cumulative genotypic resistance history should be analysed prior to any drug switch.



- ✓ Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. For example, the development of the M184V RT mutation in HIV-positive persons who fail a 3TC-containing regimen might preclude the future use of all currently available single-tablet regimens.
- ✓ HIV-positive persons should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity of the new regimen.

OTTIMIZZAZIONE

<u>Quesito clinico</u> - In pazienti in trattamento efficace con ART a 3 farmaci, il passaggio a regimi a 2 farmaci può mantenere la risposta virologica, migliorare la tollerabilità o ridurre la tossicità?

<u>Statement</u>

La soppressione virologica in pazienti in terapia efficace con regimi a tre farmaci può essere mantenuta con il cambio verso alcuni regimi a due farmaci con i seguenti livelli di raccomandazione:

a. DTG + RPV [AI];

b. ATV/r + 3TC, DRV/r + 3TC [AI per switch da PI con booster, BI per switch da altri regimi];

c. DRV/r + RAL, DRV/r + RPV [CI];

d. DTG + 3TC [BII].

SIMIT
Società Italiana di Malattie Infettive e Tropicali

In collaborazione con:

Ministero della Salute

Sezioni L e M del Comitato Tecnico Sanitario

Linee Guida Italiane sull'utilizzo della Terapia Antiretrovirale e la gestione diagnostico-clinica delle persone con infezione da HIV-1

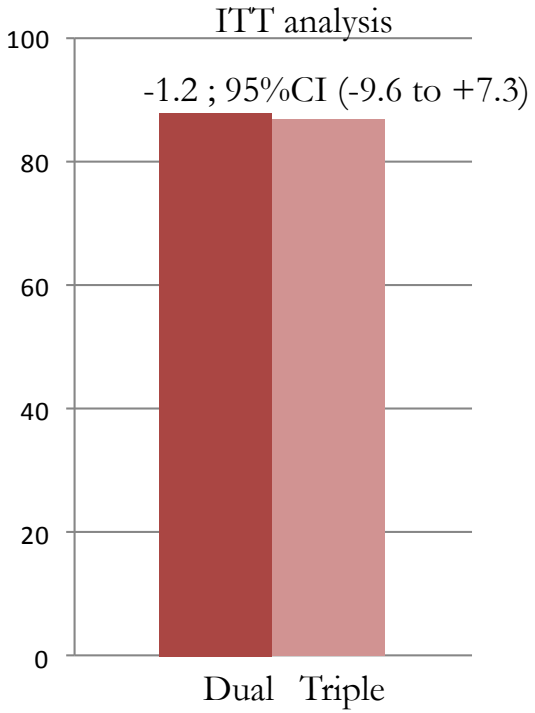
Edizione 2017

Boosted PI *plus* 3TC

HIV RNA < 50 c/ml, 48 week-data from randomized, non-inferiority (-12%) and switch studies.

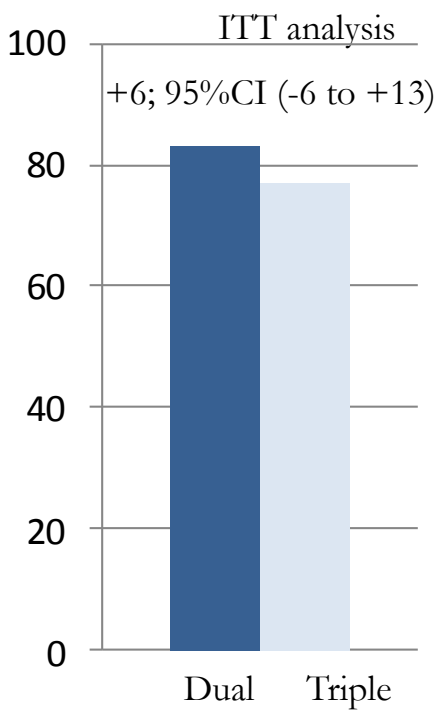
OLE study[1]

LOP/r + 2 NRTIs (121 pts)
LOP/r + 3TC od (118 pts)



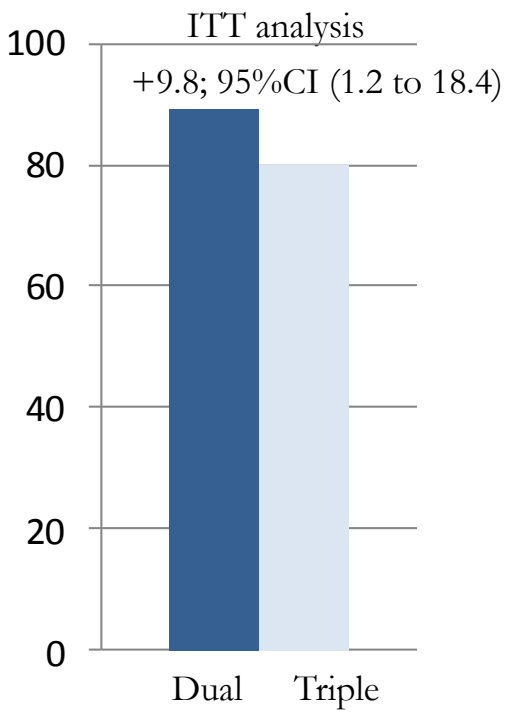
SALT study[2]

ATV/r + 2 NRTIs (143 pts)
ATV/r + 3TC od (143 pts)

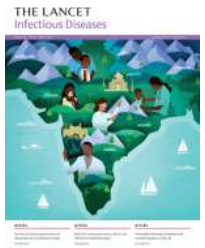


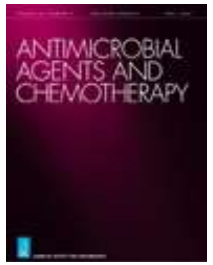
ATLAS-M study [3]

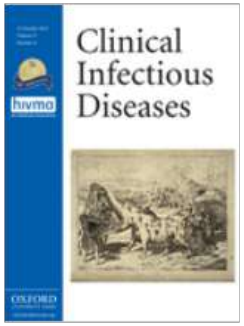
ATV/r + 2 NRTIs (133 pts)
ATV/r + 3TC od (133 pts)



1. Arribas JR et al. Lancet ID 2015; 2. Perez-Molina JA et al. Lancet ID 2015; 3. Di Giambenedetto S et al. JAC 2017





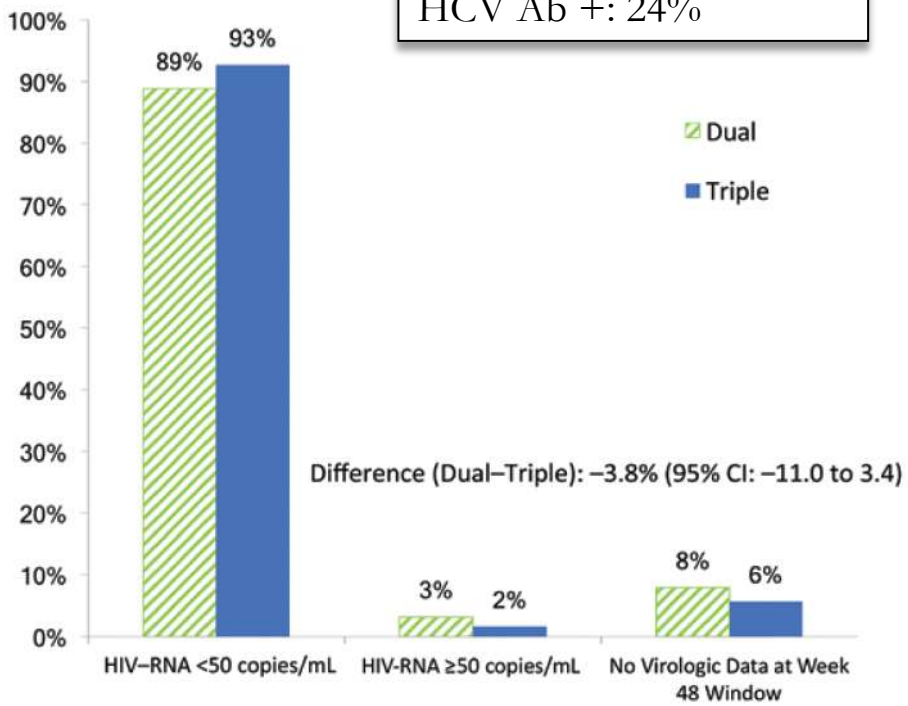


DRV/r *plus* **3TC** : DUAL GESIDA study

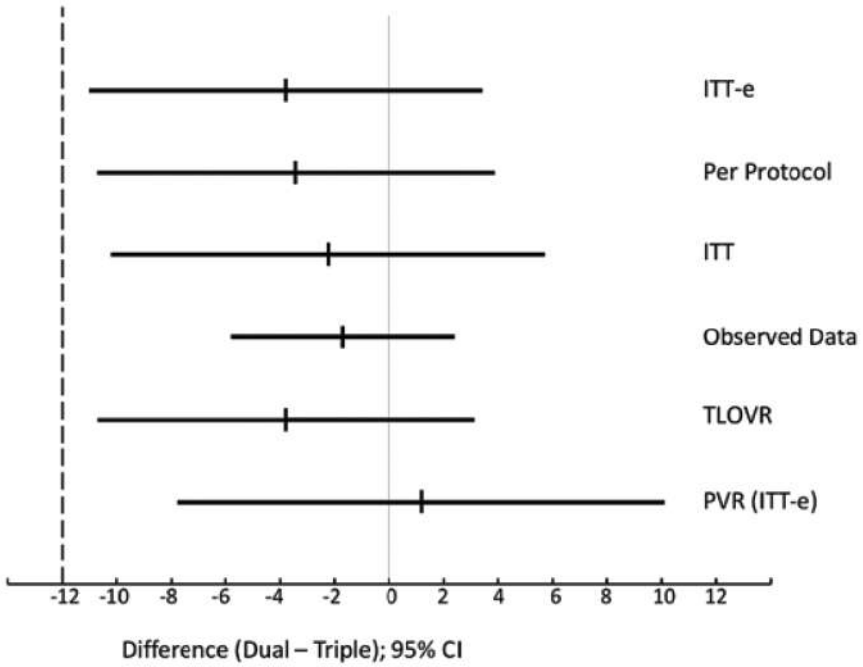
HIV RNA < 50 c/ml, 48 week-data from randomized, non-inferiority (-12%) and switch study.

Total patients: 249

On TDF at baseline: 75%
HCV Ab +: 24%



Secondary sensitivity analysis

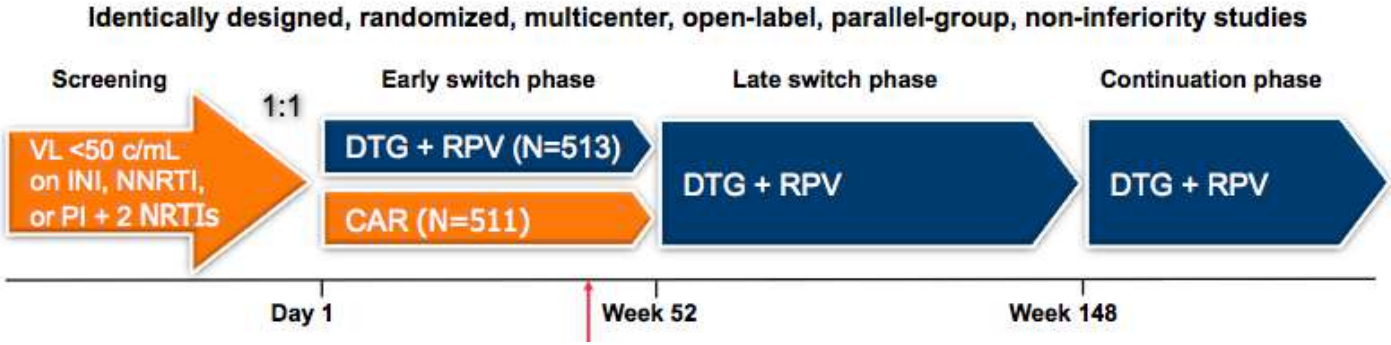


Persistent response (no failure, no blips):
85.7% *versus* 84.5% difference 1.2% (95%CI -7.8 +110.1)

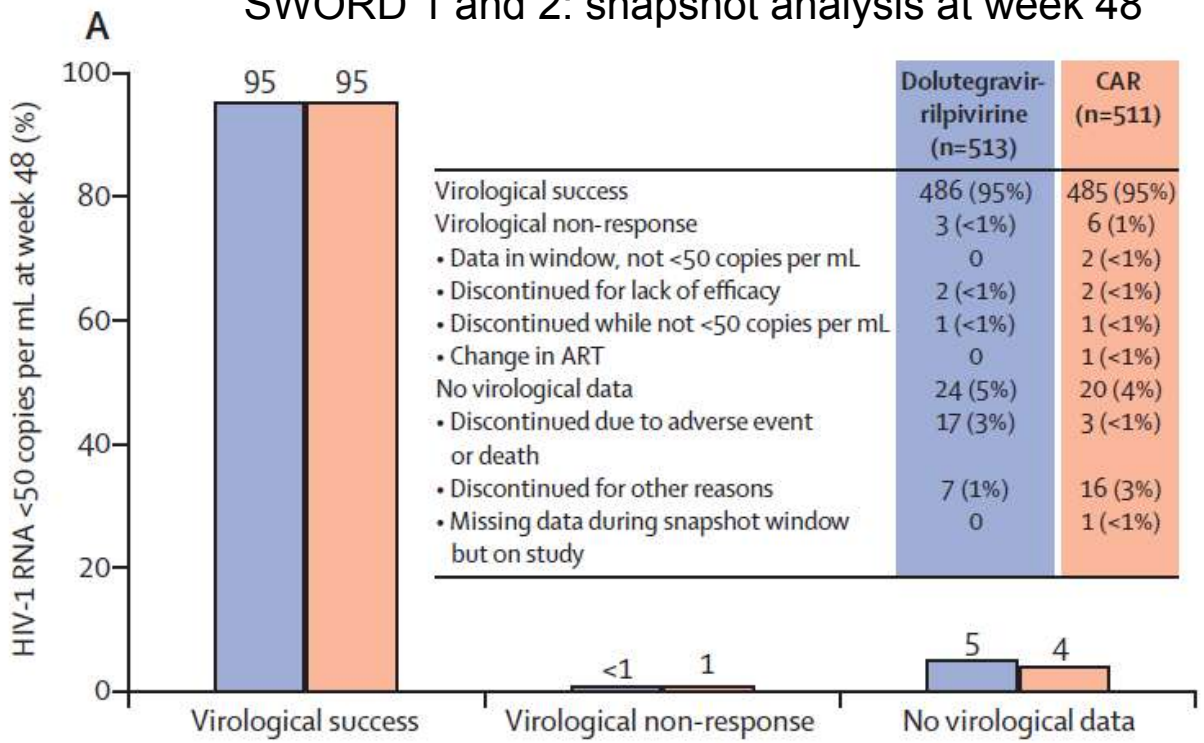
Pulido F. et al. CID 2017;65:2112-2118


THE LANCET

SWORD 1 and 2 studies



SWORD 1 and 2: snapshot analysis at week 48



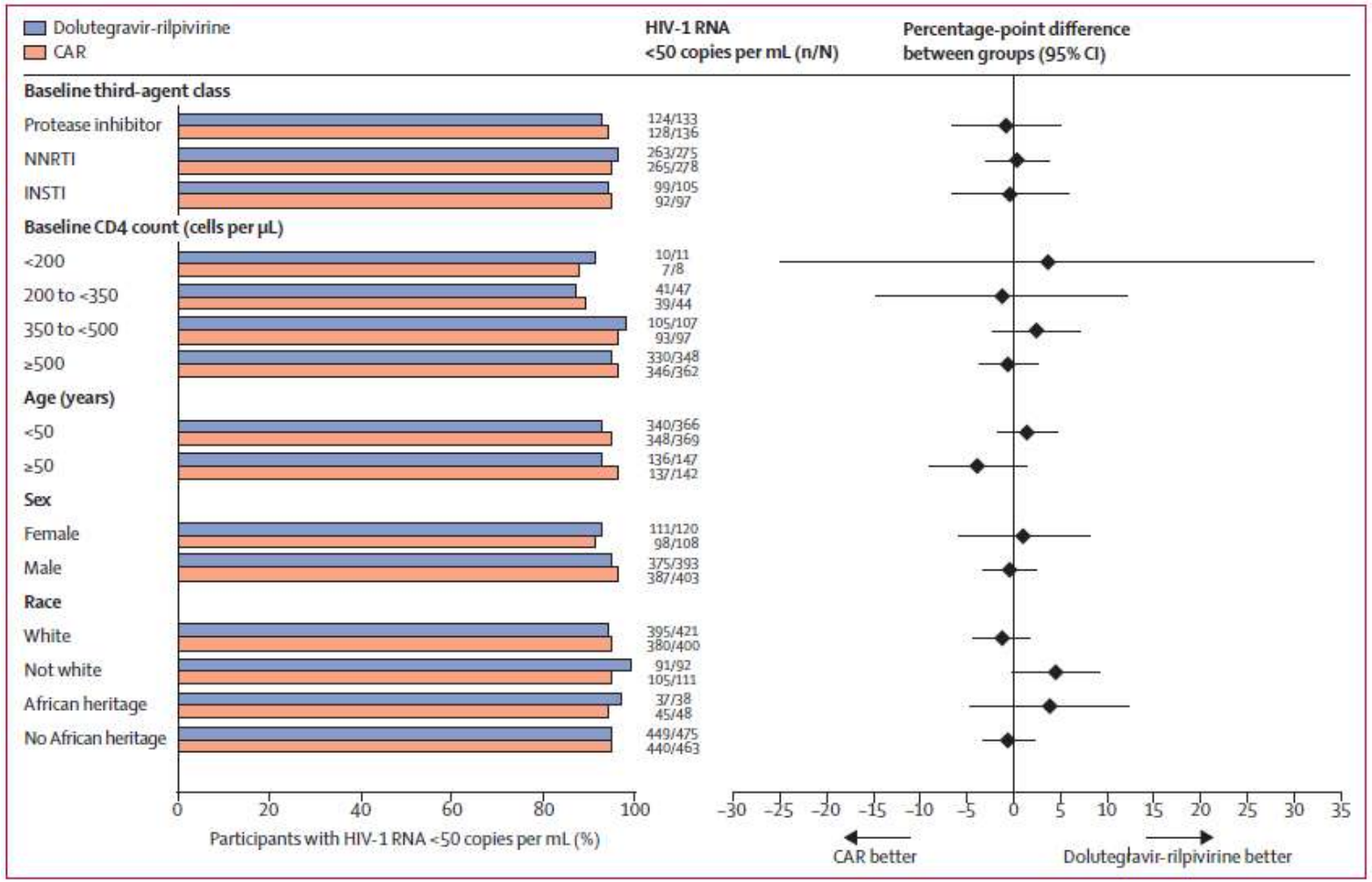
	Dolutegravir-rilpivirine (n=513)	CAR (n=511)
Virological success	486 (95%)	485 (95%)
Virological non-response	3 (<1%)	6 (1%)
• Data in window, not <50 copies per mL	0	2 (<1%)
• Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
• Discontinued while not <50 copies per mL	1 (<1%)	1 (<1%)
• Change in ART	0	1 (<1%)
No virological data	24 (5%)	20 (4%)
• Discontinued due to adverse event or death	17 (3%)	3 (<1%)
• Discontinued for other reasons	7 (1%)	16 (3%)
• Missing data during snapshot window but on study	0	1 (<1%)

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

SWORD 1 and 2 studies

Response rate at week 48 by subgroups

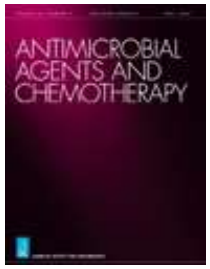
ITT analysis



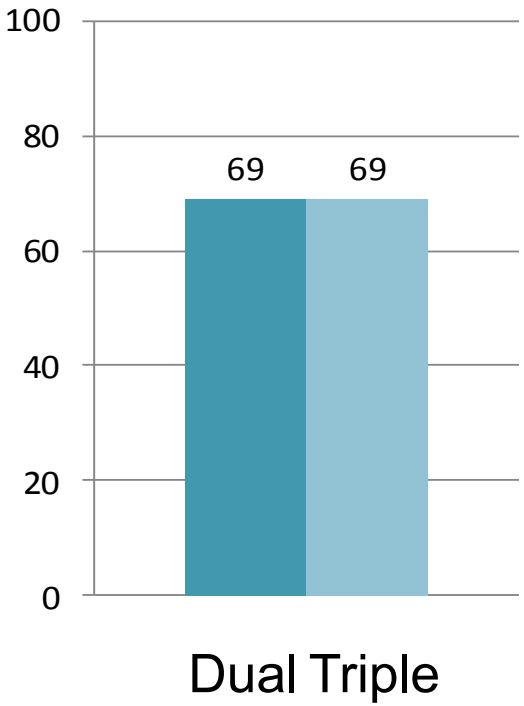
Llibre JM et al. Lancet 2018;391:839-849

Durability of bPI+3TC therapy: 96-week data

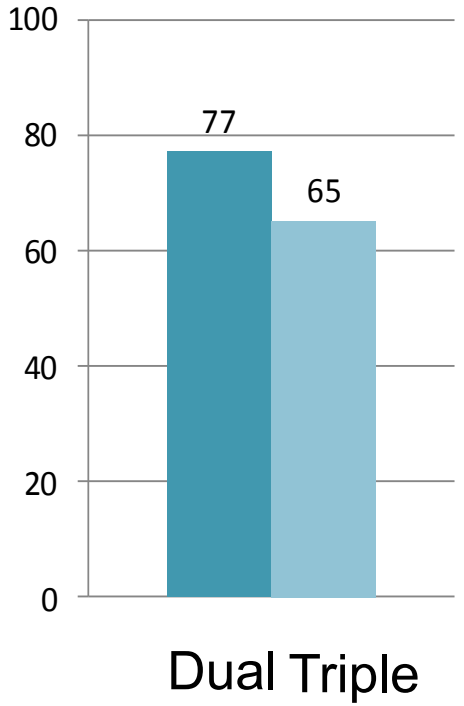
(ITT analysis, snapshot)



SALT



ATLAS-M

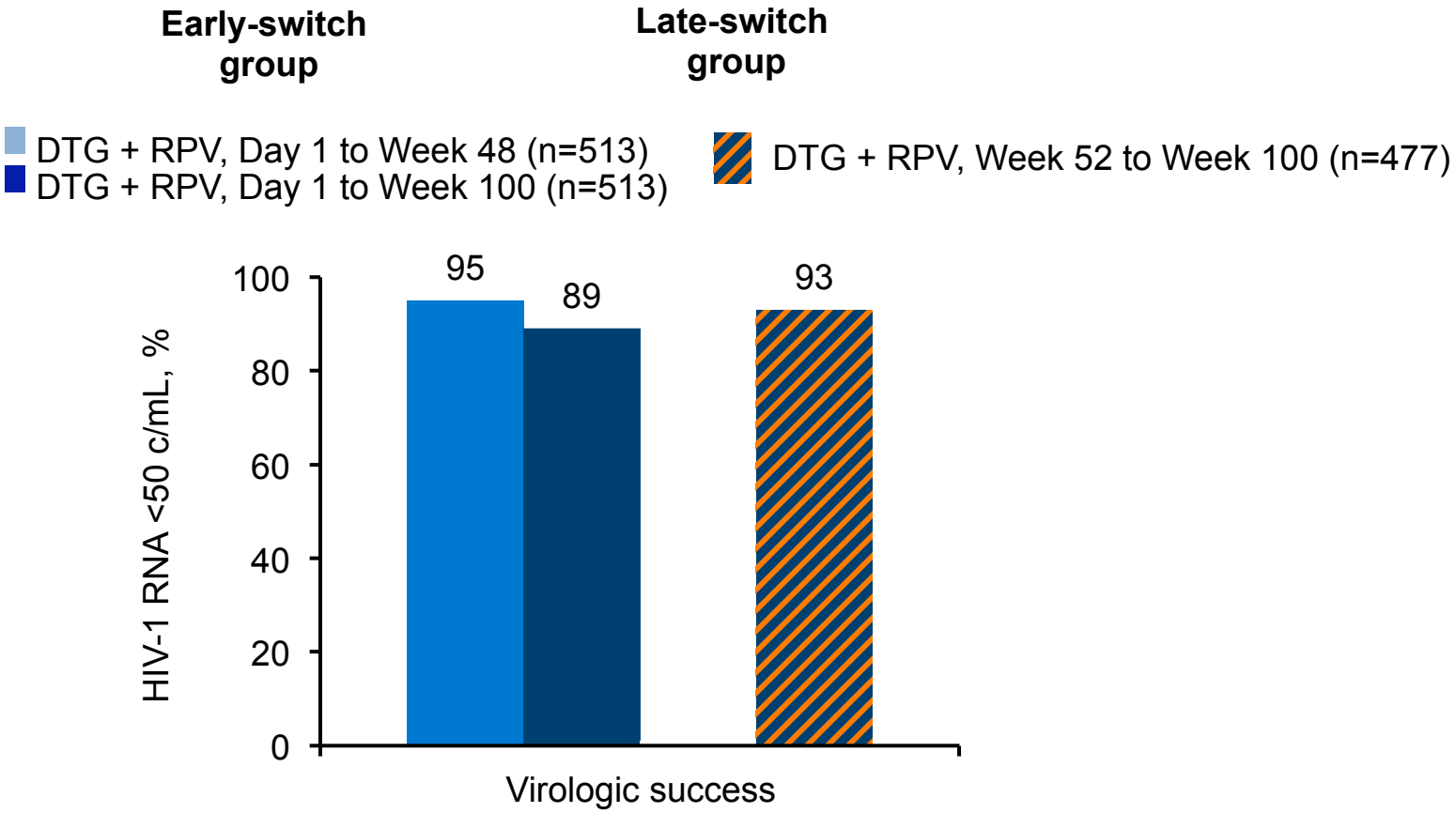


One patient taking ATV/r + 2NUCs with (M184V and L63P)

Perez-Molina et al. JAC 2017;72:246-253

Gagliardini R et al. Glasgow 2016;Abs 0121

Virologic Efficacy: 100 weeks of treatment, DTG + RPV

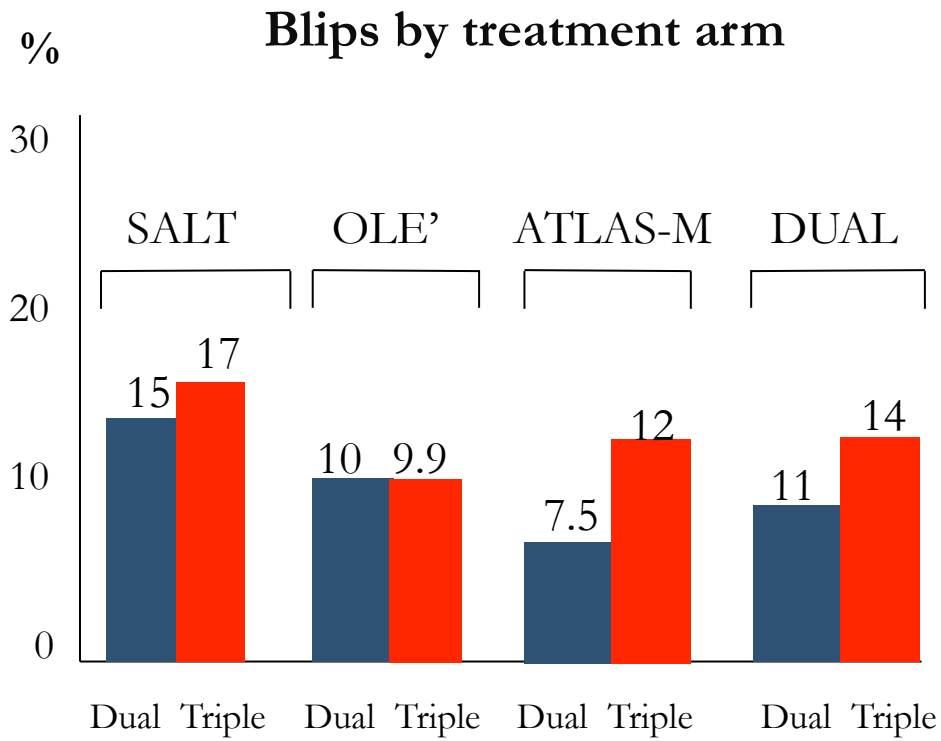


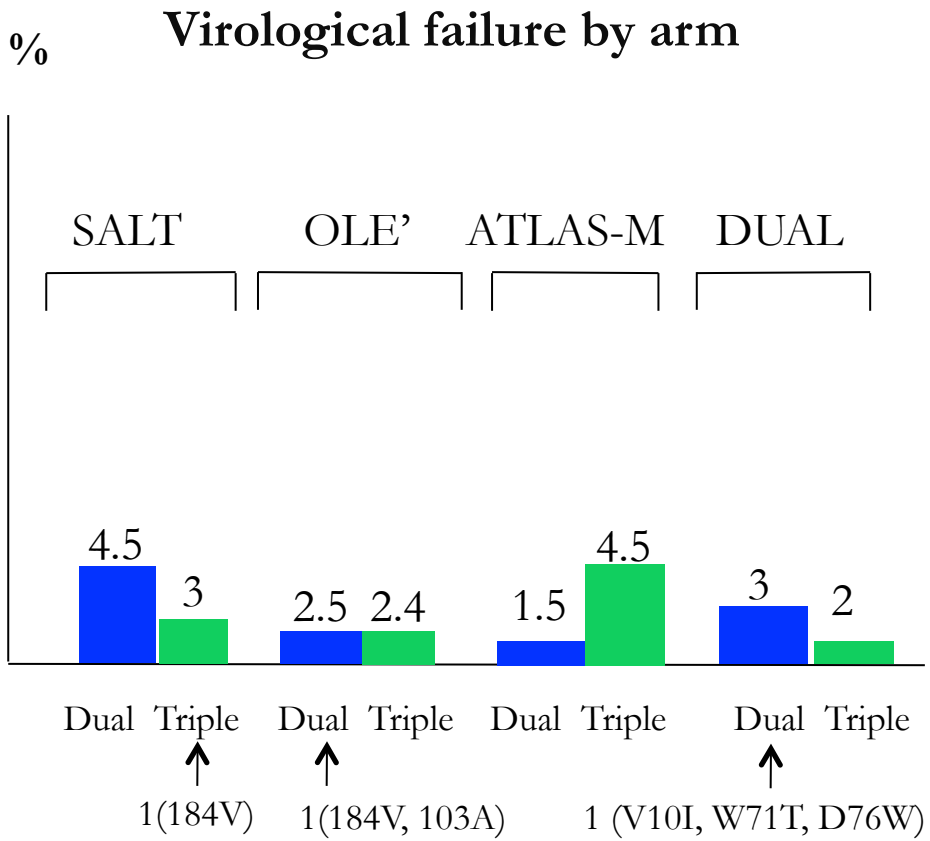
[a]Other reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

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

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

Viral blips & virological failure in dual therapy



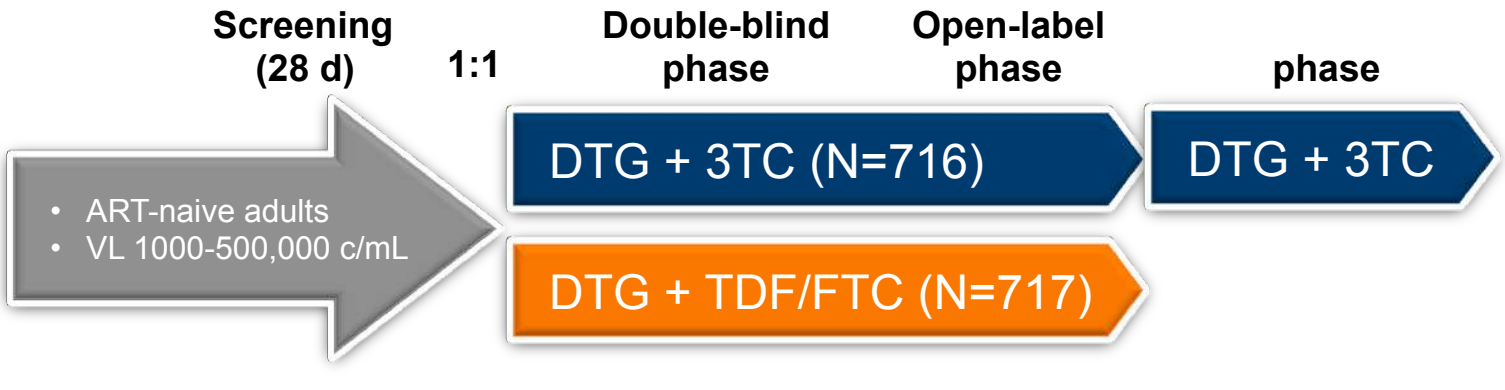


1. Perez-Molina JA et al. Lancet ID 2015;
2. 2. Arribas JR et al. Lancet ID 2015;

3. DUAL GESIDA, CID 2017

GEMINI-1 and -2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies



Eligibility criteria
- ≤10 days of prior ART
- No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
- No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E snapshot)[a]

Countries

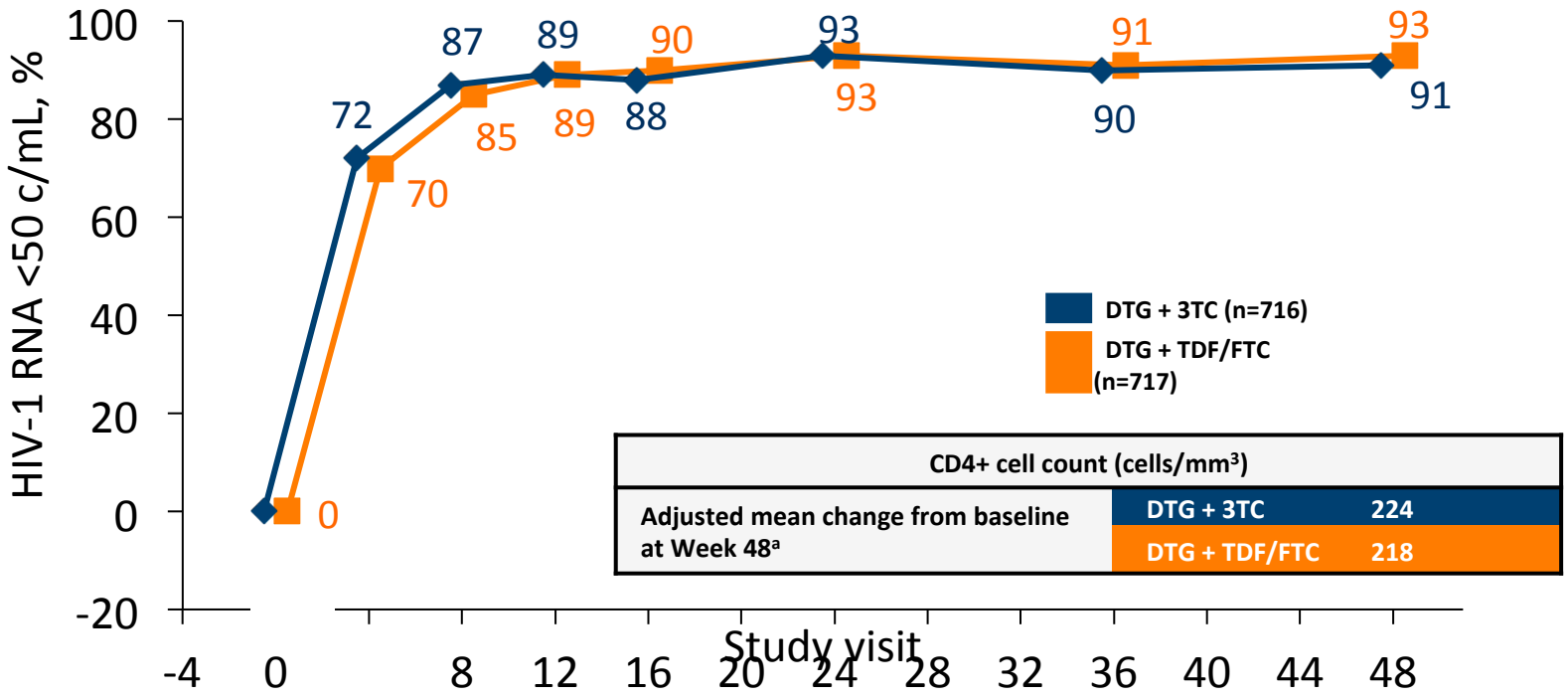
Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3).

[a]–10% noninferiority margin for individual studies.

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

Snapshot Analysis by Visit: Pooled ITT-E Population

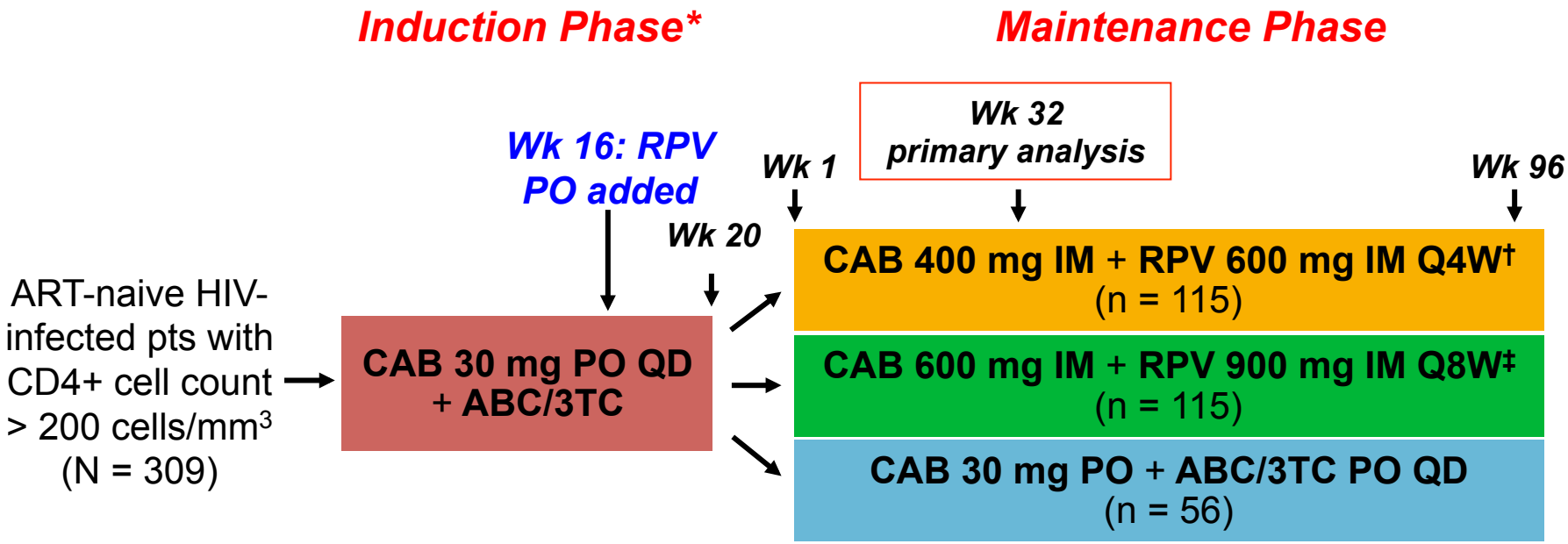


[a]Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

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

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label phase IIb study
  - Cabotegravir: integrase inhibitor



6 pts discontinued for AEs or death in induction analysis. *Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. †Loading dose: Day 1, CAB 800 mg + RPV 600 mg. ‡Loading

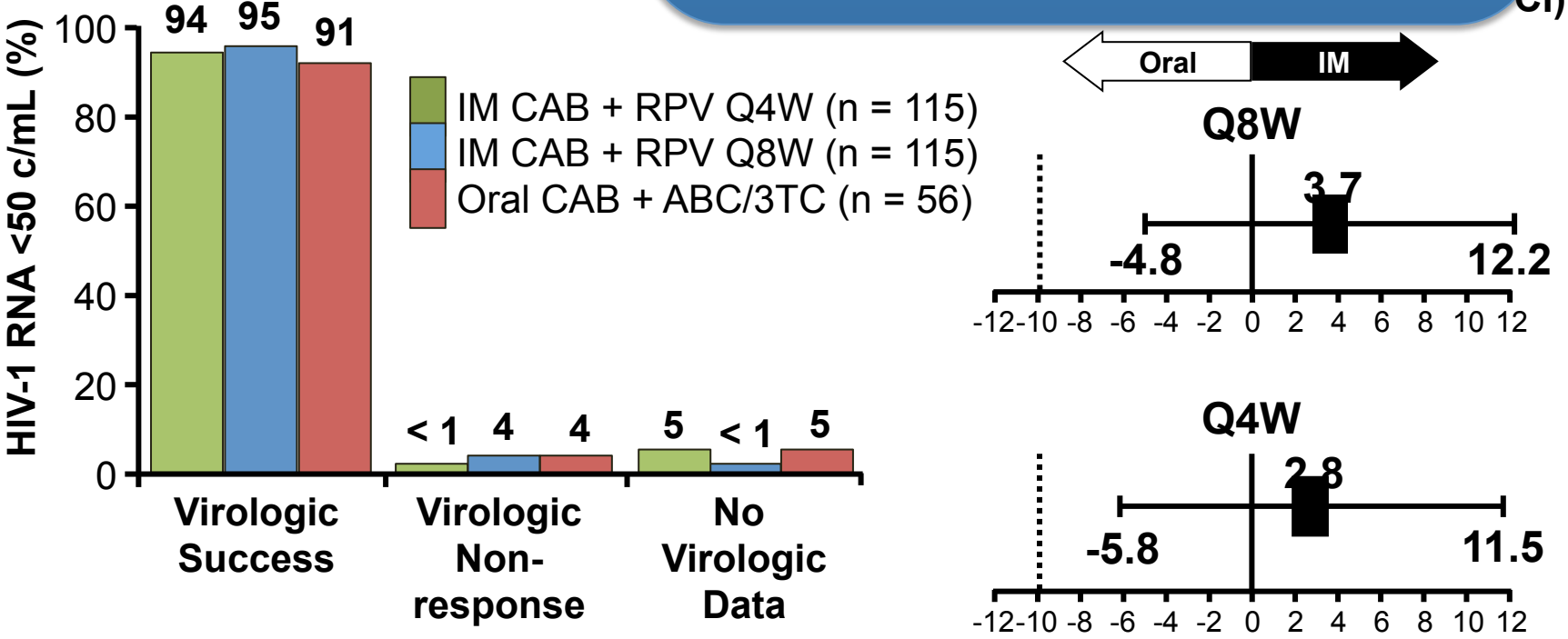
Margolis DA, et al. CROI 2016. Abstract 31LB.

LATTE-2: Mainte… … Efficacy (ITT-M…

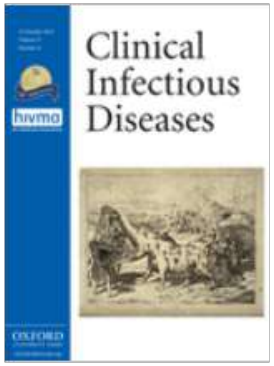
- Virologic efficacy of Q4W … …men

Only 2 patients met criteria for protocol-defined virologic failure (1 oral CAB and 1 IM CAB Q8W) and neither patient had resistance to NRTI, NNRTI, or integrase.

…CI)

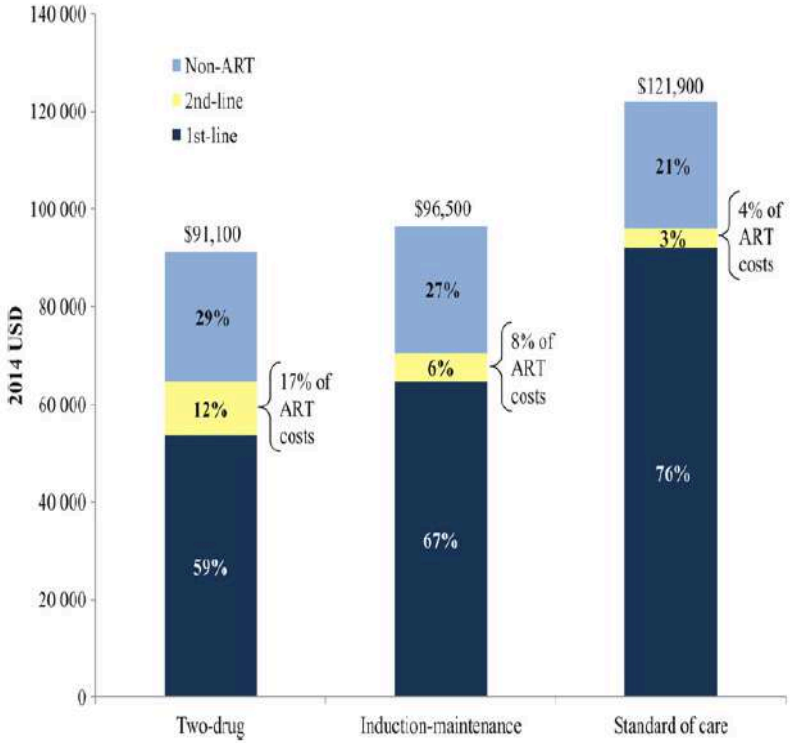


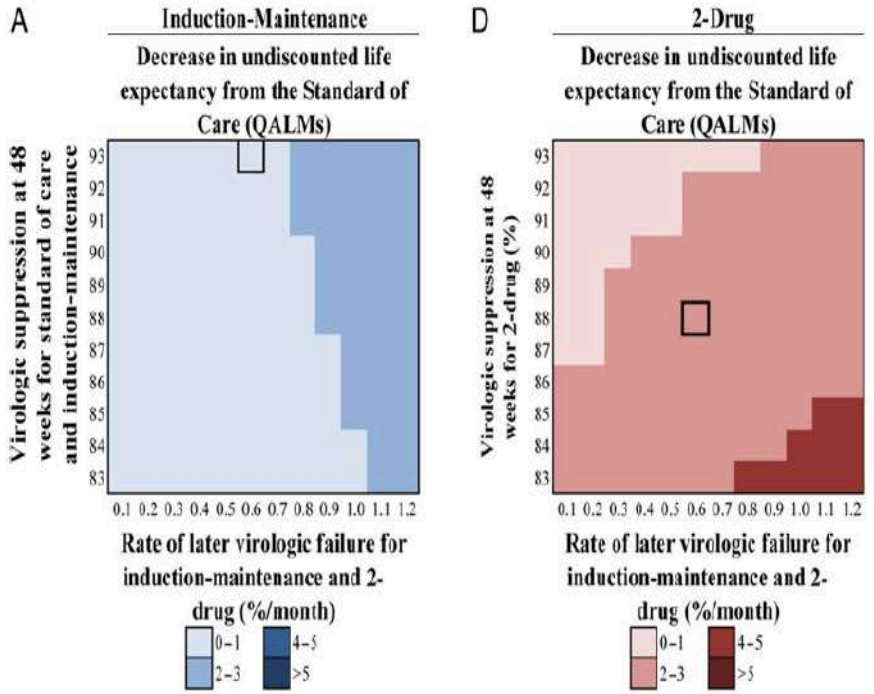
Margolis DA, et al. CROI 2016. Abstract 31LB.



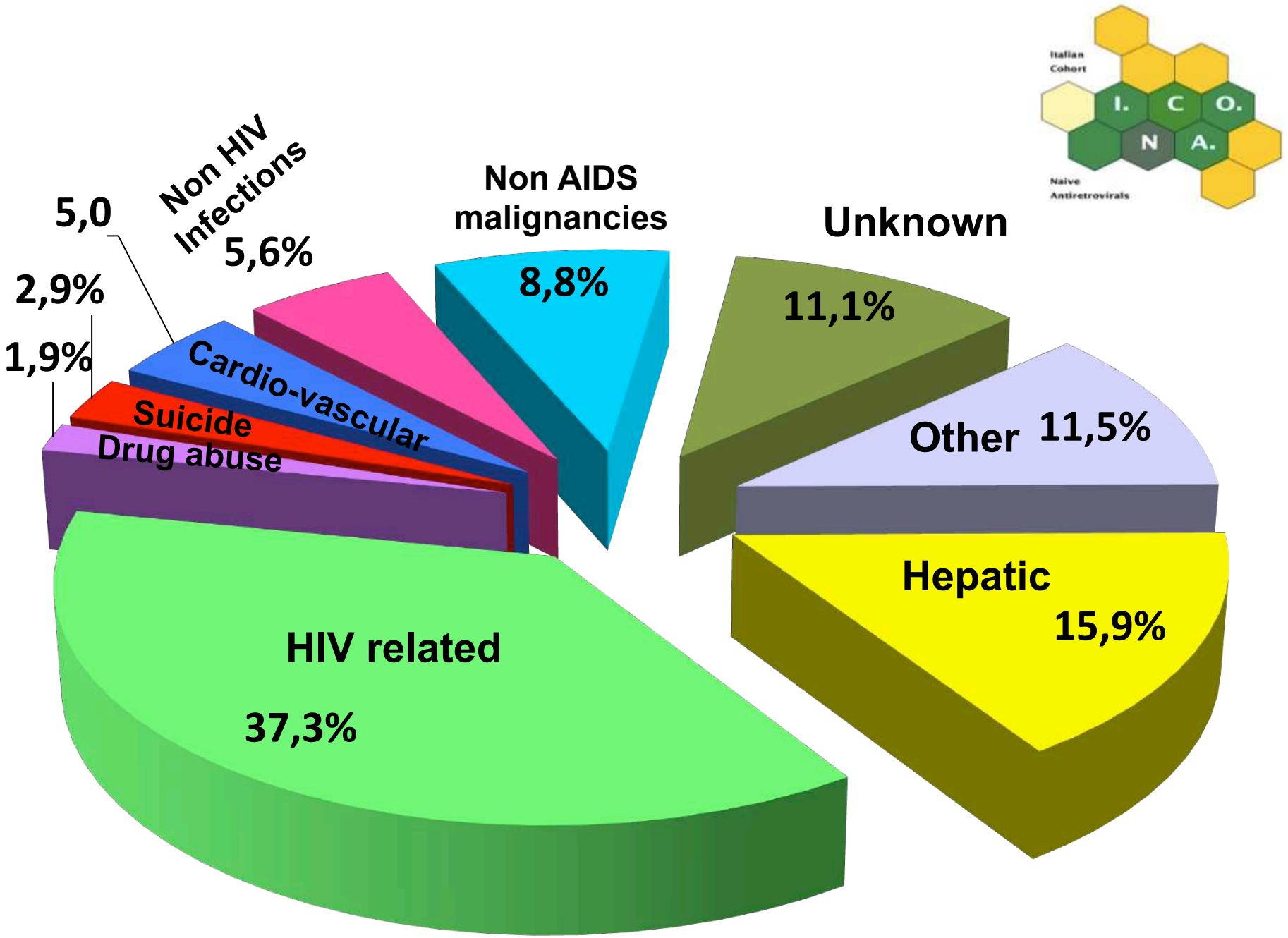
Cost-effectiveness and Budget Impact of DTG+3TC 2DR for the Treatment of HIV Infection in the US

With 50% uptake of either induction-maintenance or **2-drug for ART-naive patients**, cost savings totaled $550 million and **$800 million**, respectively, within 5 years; **savings reached >$3 billion if 25% of currently suppressed patients were switched to DTG + 3TC maintenance.**





Girouard MP, et al. Clin Infect Dis, 2016



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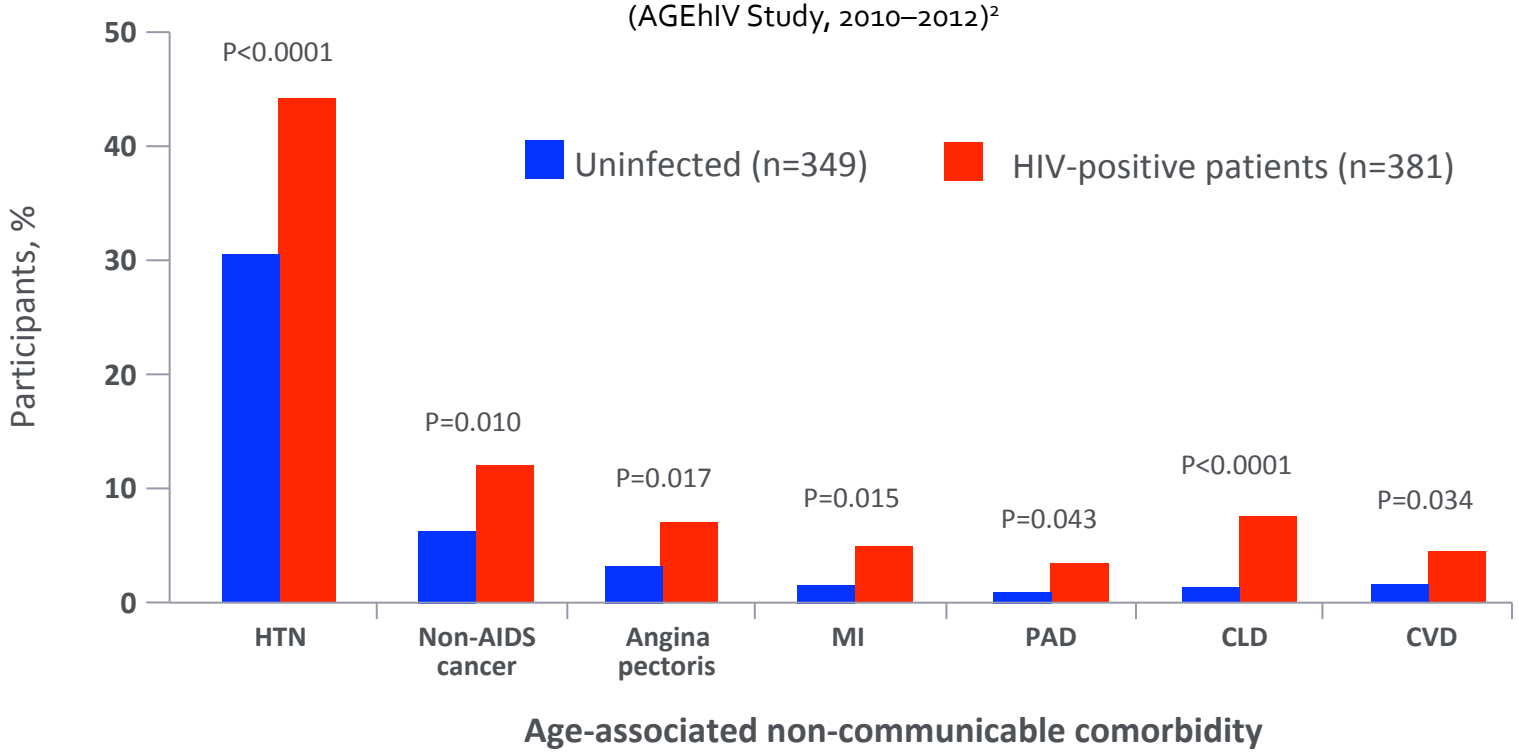
Comorbidities are more prevalent in HIV-positive patients

- HIV infection may compress certain ageing processes, accelerating comorbidities and frailty[1]
- Duration of ART use (OR 1.24 per 5 additional years of ART use) and lower nadir CD_4 count (OR 1.12 per 100 less cells) were associated with an increased risk of a higher number of comorbidities

Subjects ≥45 years with age-associated non-communicable comorbidities, by HIV serostatus
(AGEhIV Study, 2010–2012)[2]

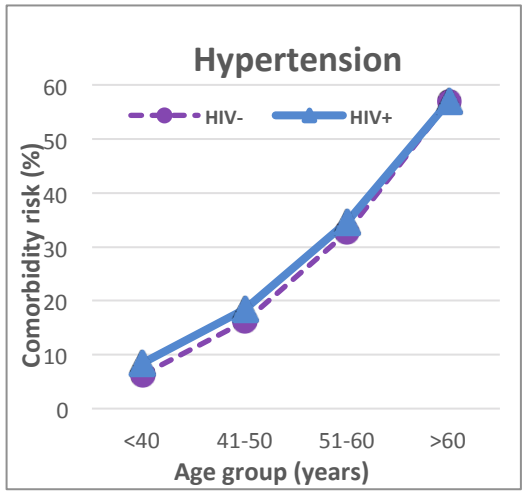


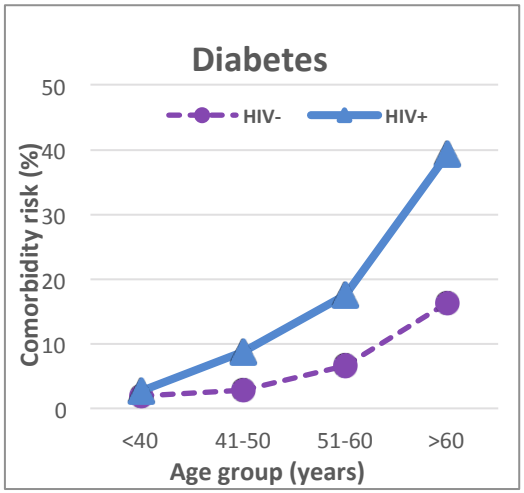
CLD, chronic liver disease; CVD, cerebrovascular disease; HTN, hypertension; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease

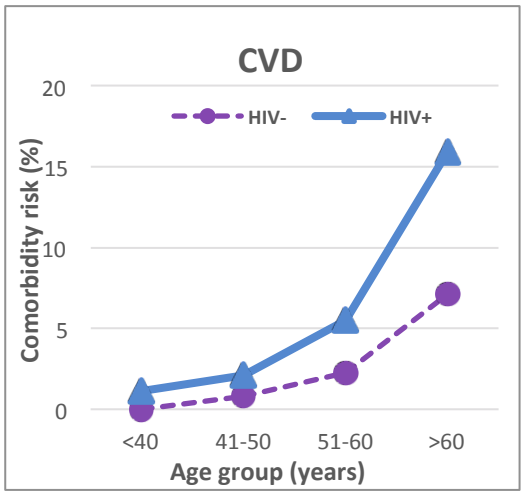
1. Effros RB et al. Clin Infect Dis 2008;47:542–553; 2. Schouten J et al. IAC 2012. Washington, DC. THAB0205

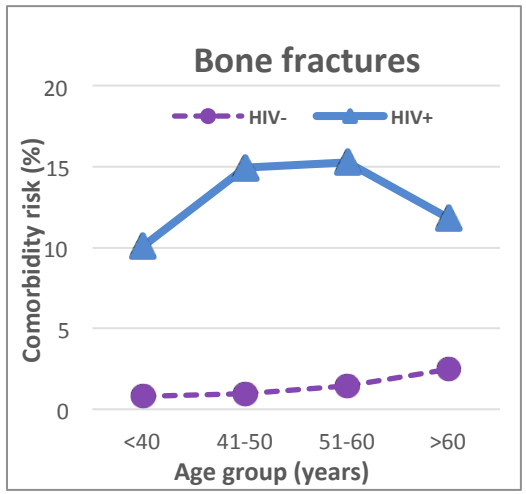
With increased life expectancy, management of non-HIV related comorbidities is now a significant area of focus

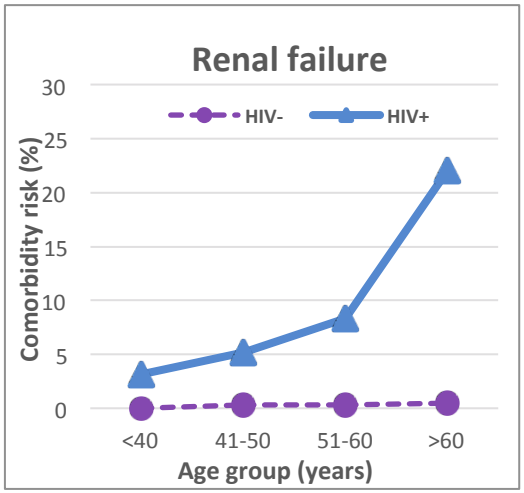
- **Patients with HIV are more susceptible to developing cardiovascular disease, bone fractures and renal failure than HIV-negative[2]**
  - In the 41–50-year-old cohort, HIV-positive patients are 24x more likely to develop renal failure; this increases to 63x for the >60-year-old cohort [1]
  - Bone fracture risk ranged between 12–16x more likely for HIV-positive vs uninfected in the <40–60-year-old range[1]
- **These comorbidities often develop earlier in HIV-positive patients[2]**











1. Adapted from Guaraldi G et al. Clinicoecon Outcomes Res 2013;5:481–488;
2. Guaraldi G et al. Clin Infect Dis 2011;53:1120–1126

ID-651

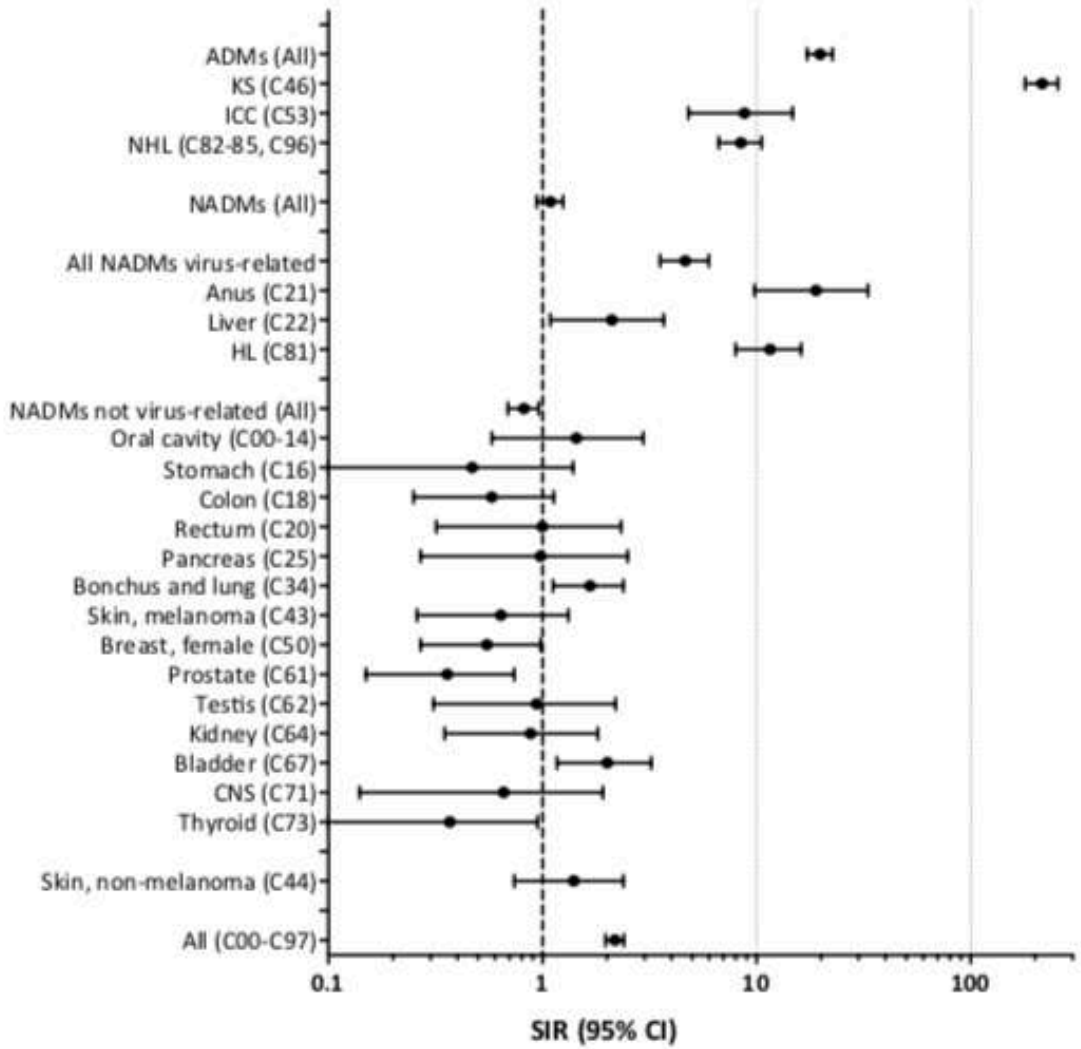
STILL HIGH RISK OF VIRUS-RELATED CANCER DESPITE 20 YEARS OF cART IN ICONA COHORT

Pierluca Piselli[1], Diego Serraino[2], Alessandra Bandera[3], Andrea Antinori[1], Enrico Girardi[1], Claudia Cimaglia[1], Alessandro Tavelli[4], Francesca Bai[5], Gianmaria Baldin[6], Andrea Calcagno[7], Antonella D'Arminio Monforte[5], Antonella Cingolani[6], for the Icona Foundation Study Group

[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, [2]CRO Aviano National Cancer Institute, Aviano, [3]San Gerardo Hospital, Monza, [4]Icona Foundation, Milan, [5]University of Milan, Milan, [6]Catholic University of the Sacred Heart, Rome, [7]University of Turin

CROI 2018
Boston, March 4–7, 2018

Fig. 3. Standardized incidence ratios (SIR) and 95% Confidence Intervals (CI) for selected cancers



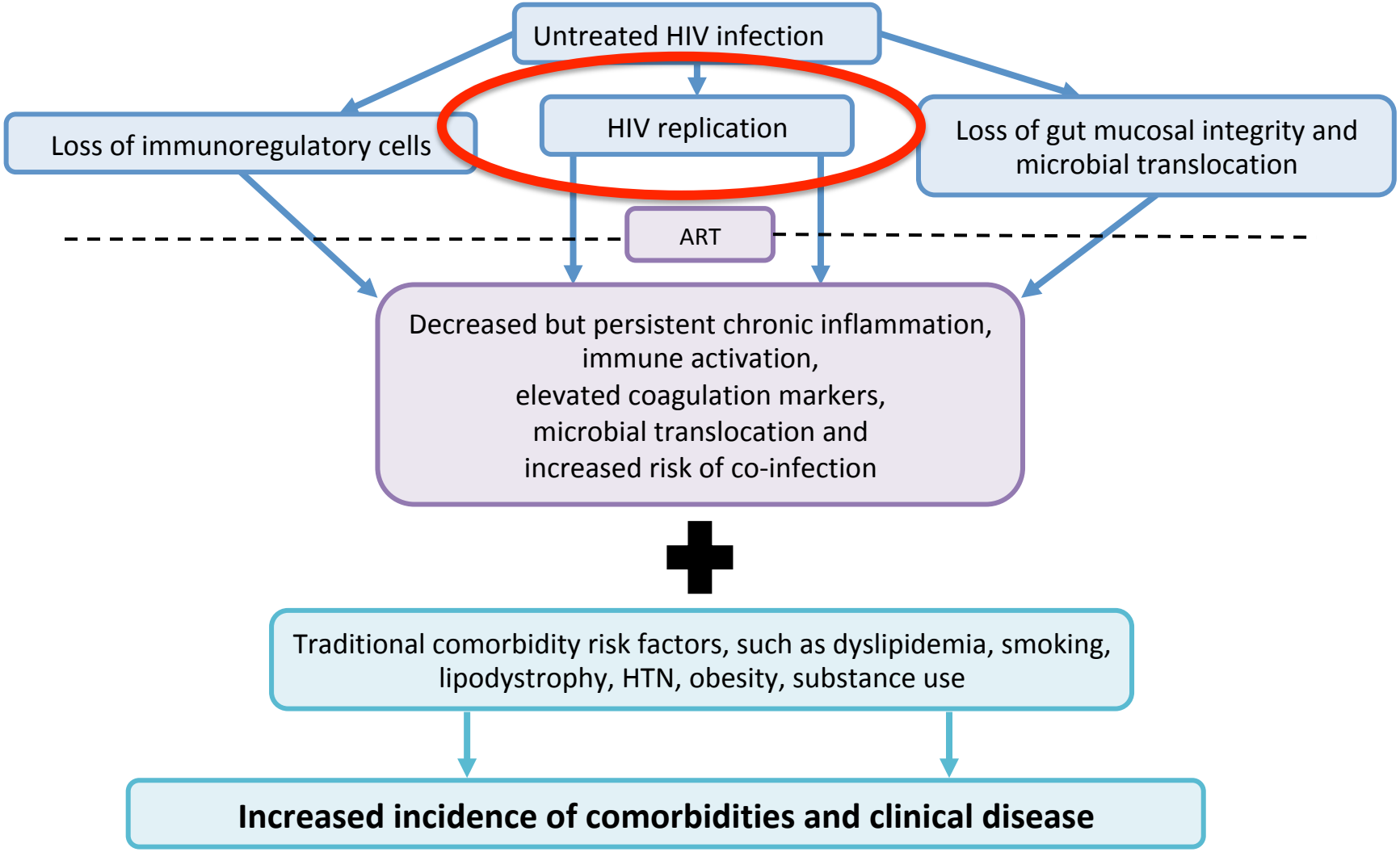
A substantial higher incidence of cancer compared to general population was observed (2.2-fold increased risk for all cancers).

Despite a decline over time for ADMs, risk of virus-related cancers remains elevated in the modern treatment era

AIDS-defining malignancies (ADMs, i.e. Kaposi sarcoma-KS, Non-Hodgkin lymphoma-NHL and Invasive Cervical Cancer-ICC)

non-AIDS defining malignancies (NADMs)

Chronic inflammation is associated with increased risk for comorbidities in HIV-positive patients



Deeks SG. Annu Rev Med 2011;62:141–155

OPEN ACCESS Freely available online October 2008 | Volume 5 | Issue 10 | e203 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

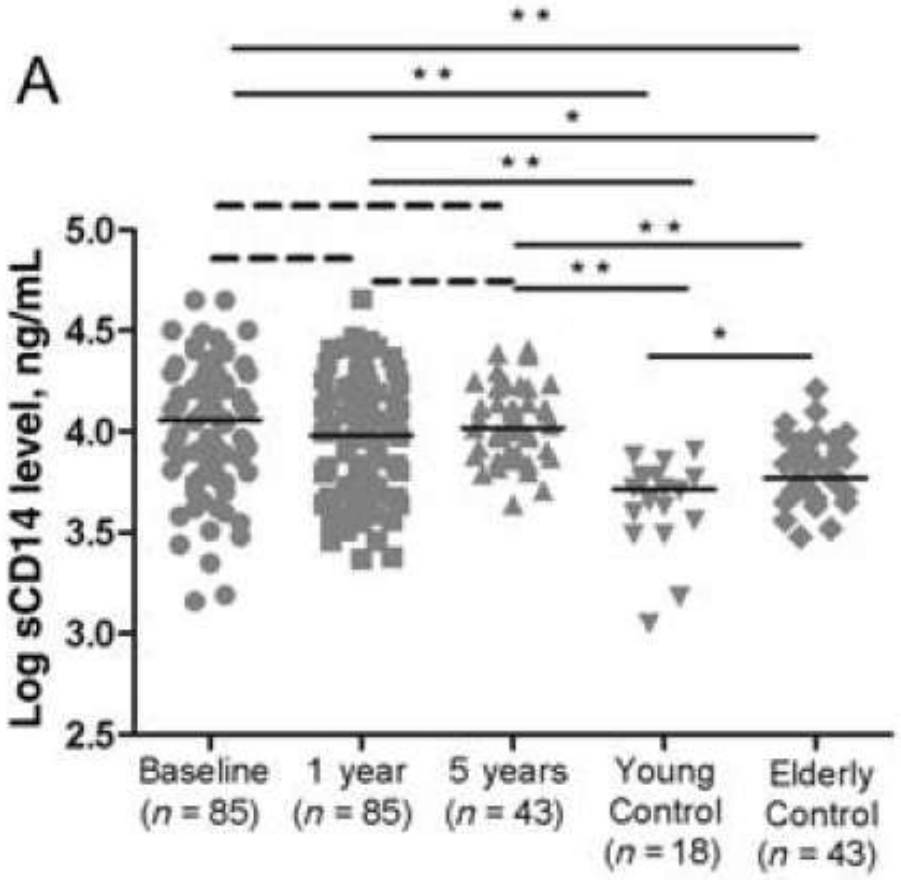
1 University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **2** University of Vermont, Burlington, Vermont, United States of America, **3** Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, **4** Saint-Pierre Hospital, Brussels, Belgium, **5** National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia, **6** National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, United States of America, **7** University Hospital, Zurich, Switzerland, **8** University of Copenhagen, Copenhagen, Denmark, **9** University of Minnesota, Minneapolis, Minnesota, United States of America, **10** Virginia Commonwealth University, Richmond, Virginia, United States of America, **11** Medical Research Council Clinical Trials Unit, London, United Kingdom

Biomarker and All-Cause Mortality Associations

Baseline Level	**OR (4^{th}/1^{st} QRT) Univariate**	*P-value*
D-dimer	**12.4**	<0.0001
IL-6	**8.3**	<0.0001
hsCRP	**2.0**	0.05

February 4, 2013

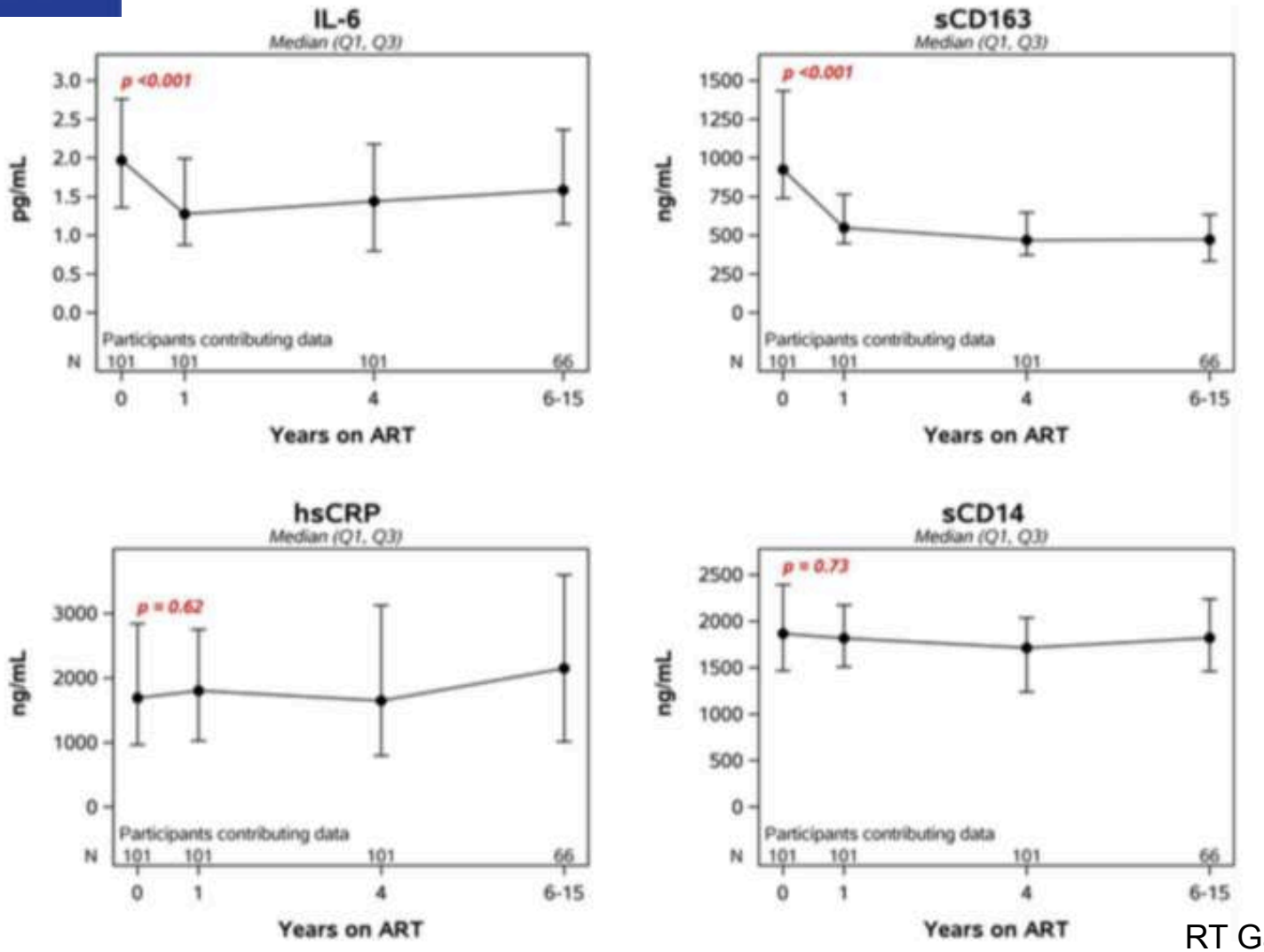
Long-Term Suppressive Combined Antiretroviral Treatment Does Not Normalize the Serum Level of Soluble CD14



HIV-infected group displayed a significantly higher sCD14 level at baseline (ie, before cART initiation), 1 year and 5 years after cART initiation, compared with both control groups.

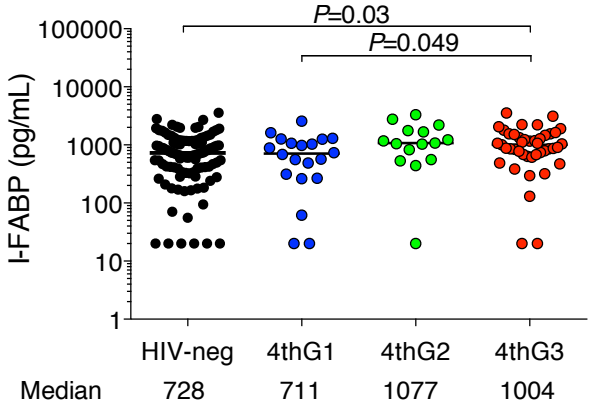
G. Mendez-Lagares

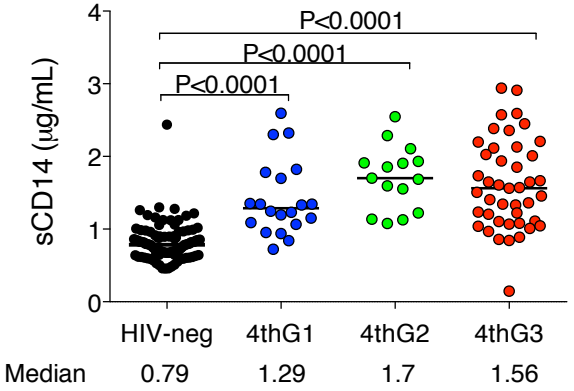
Longitudinal changes in markers of inflammation after initiation of antiretroviral therapy. The p-value in each panel is for the change in the log-transformed level of the specified biomarker from pre-ART to year 1.

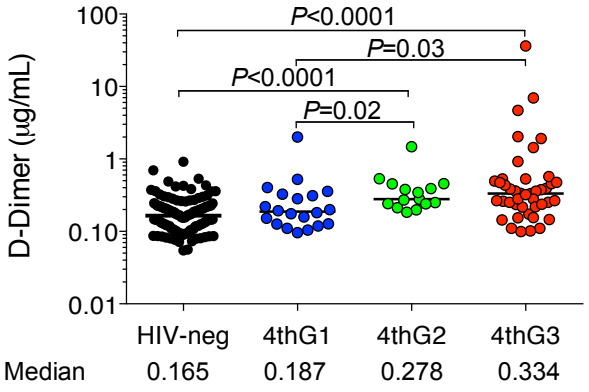


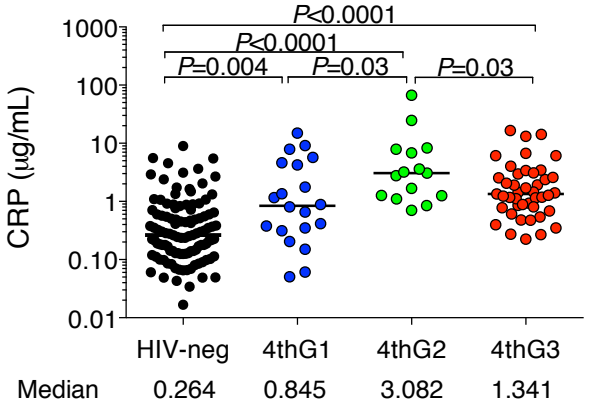
RT Gandhi, 20 april 2017

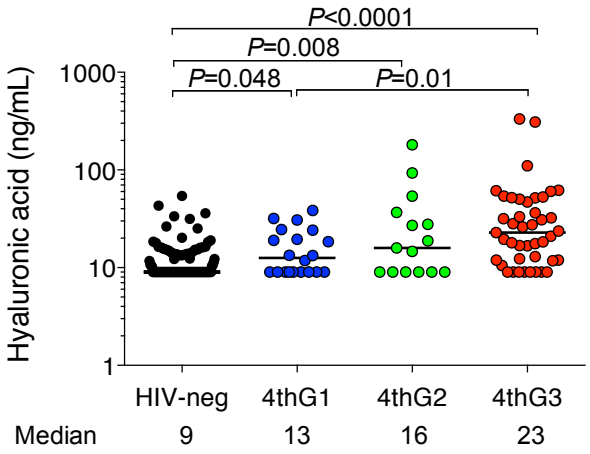
Inflammatory Biomarkers at Diagnosis of Acute HIV Infection









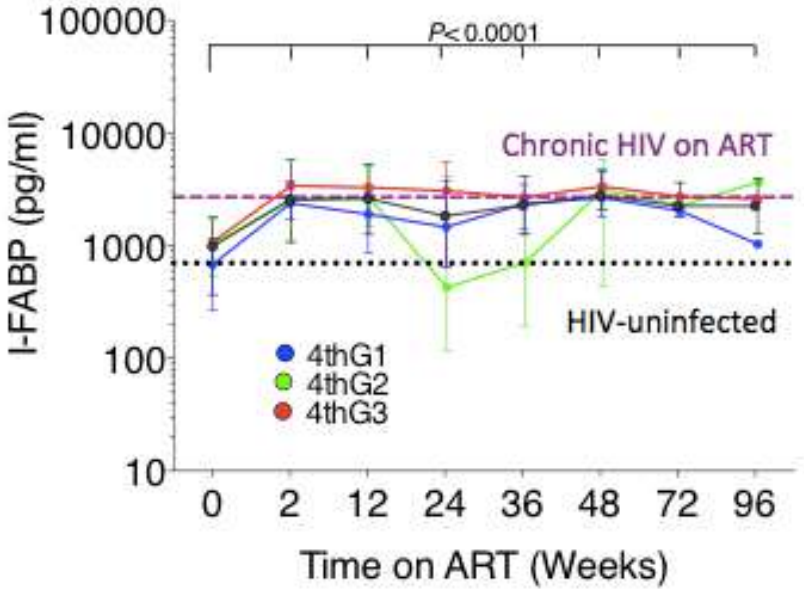


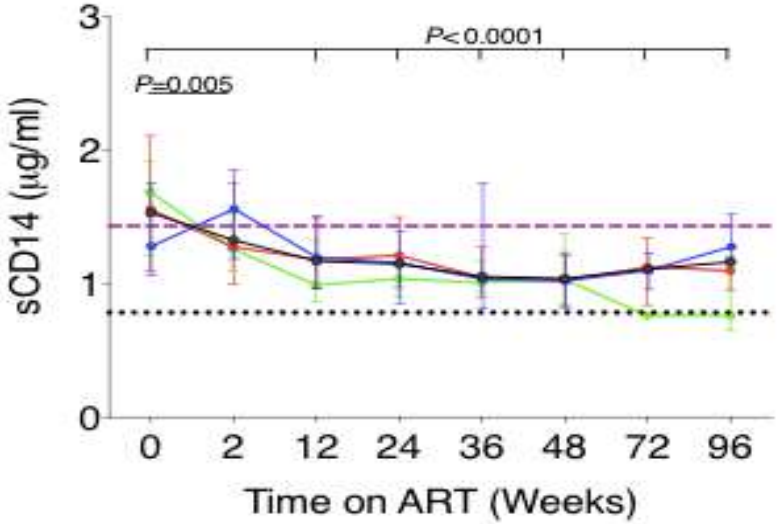
Compared to healthy controls, subjects with all stages of acute HIV infection have increased CRP, sCD14, and HA levels, and subjects with later stages of acute HIV infection have increased D-dimer and I-FABP levels.

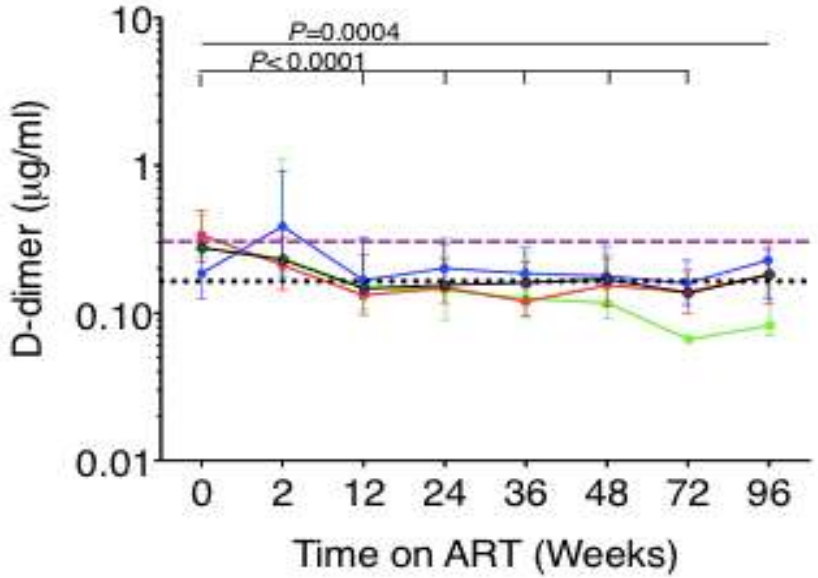
Sandler, CROI, 2014

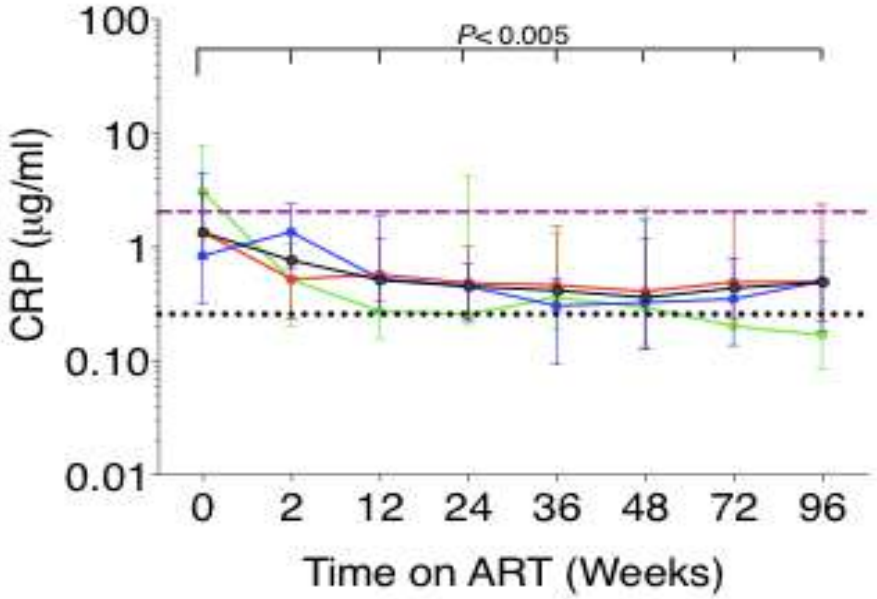
Inflammation persists despite early initiation of ART in acute HIV infection

NS Utay, CROI 2015









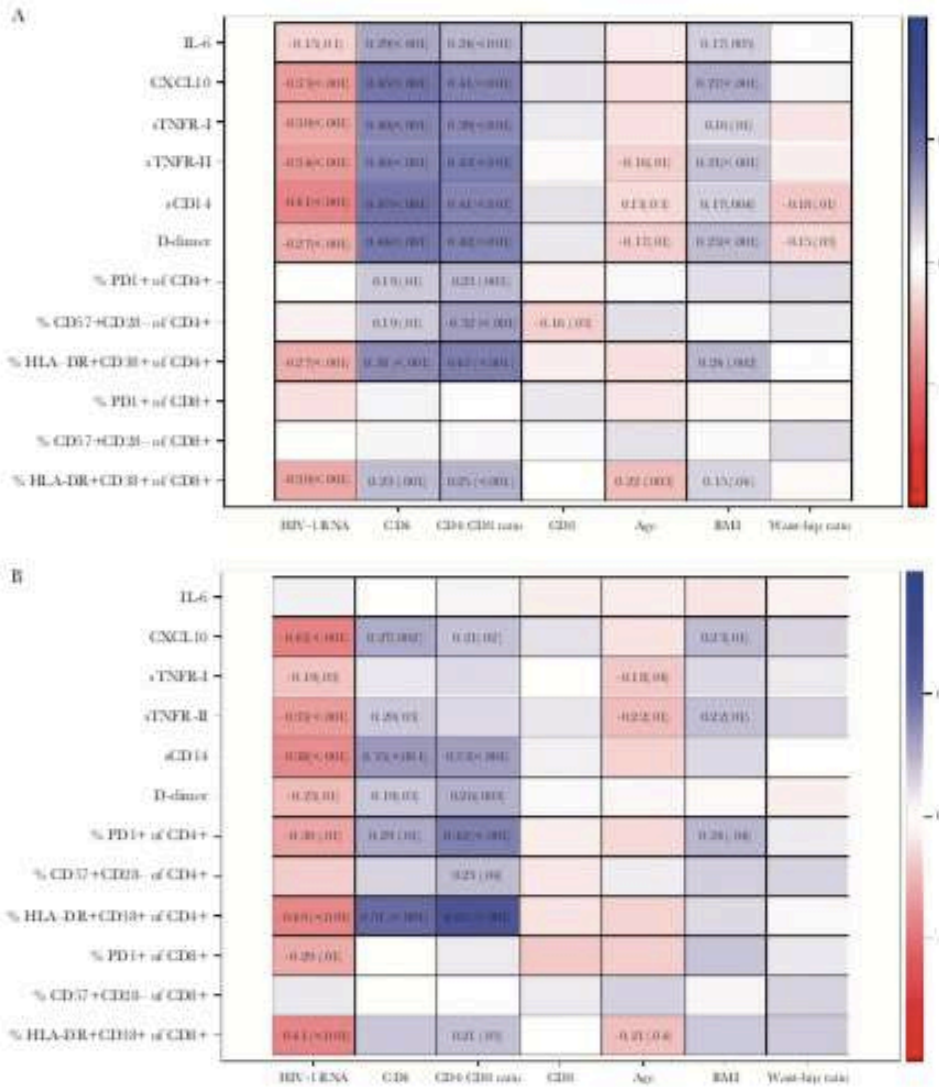
Changes in Inflammation but Not in T-Cell Activation Precede Non-AIDS-Defining Events in a Case-Control Study of Patients on Long-term Antiretroviral Therapy

Michael M. Lederman 2018;218:239–48

143 HIV–infected adults who developed a non-AIDS event at a median of 2.9 (1.7–4.6) years after ART initiation; 21 nonaccidental deaths (2 fatal MIs, 1 fatal stroke, 2 cases of fatal malignancies, 3 fatal serious bacterial infections, and 13 other nonaccidental deaths), 23 nonfatal MIs; 15 nonfatal strokes; 50 nonfatal malignancies and 34 nonfatal bacterial infections.
315 controls remained event-free.

Specimens were tested pre-ART, year 1 post-ART, and at the visit preceding the event.
Inflammatory and most activation biomarkers declined from pre-ART to year 1 for cases and controls.

Correlations (P values) of pre–antiretroviral therapy (ART) factors with changes of biomarkers. Soluble and T-cell biomarkers from pre-ART to year 1 for the controls (A) and from pre-ART to year 1 for the cases (B). Negative correlations in red and positive in blue.

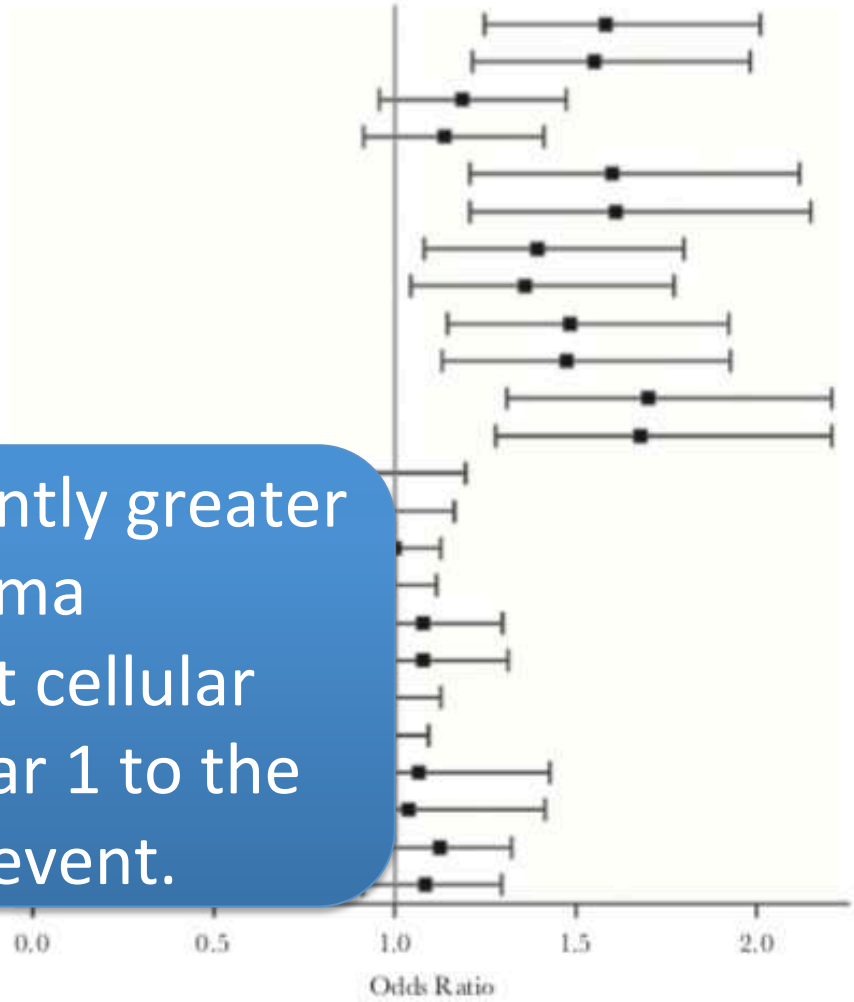


Higher pre-ART HIV RNA levels were associated with greater declines for all biomarkers (P ≤ .01).

M.M. Lederman 2018;218:239–48

Odds ratios per interquartile range of having a non-AIDS-defining event for biomarker changes from year 1 to the pre-event time. Adjusted analyses controlled for concurrent CD4+ T-cell count. *P = .01 to <.05; **P < .01.

Biomarker	Analysis	OR (95% CI)	*P* value
IL-6	Unadjusted	1.58 (1.25, 2.01)	<.001**
	Adjusted	1.55 (1.21, 1.98)	<.001**
CXCL10	Unadjusted	1.19 (.96, 1.47)	.123
	Adjusted	1.13 (.91, 1.41)	.258
sTNFR-I	Unadjusted	1.60 (1.21, 2.12)	.001**
	Adjusted	1.61 (1.21, 2.15)	.001**
sTNFR-II	Unadjusted	1.39 (1.08, 1.80)	.011*
	Adjusted	1.36 (1.04, 1.77)	.023*
sCD14	Unadjusted	1.48 (1.14, 1.92)	.003**
	Adjusted	1.47 (1.13, 1.92)	.004**
D-dimer	Unadjusted	1.70 (1.31, 2.21)	<.001**
	Adjusted	1.68 (1.28, 2.21)	<.001**
		0.87 (.64, 1.19)	.395
		0.83 (.60, 1.16)	.287
		1.00 (.88, 1.13)	.977
		0.98 (.87, 1.11)	.786
		1.08 (.89, 1.30)	.433
		1.08 (.88, 1.31)	.469
		0.92 (.75, 1.13)	.412
		0.87 (.70, 1.09)	.237
		1.07 (.80, 1.43)	.672
		1.04 (.76, 1.42)	.822
		1.12 (.95, 1.32)	.164
		1.08 (.91, 1.29)	.370



Cases, had significantly greater increases in all plasma biomarkers (but not cellular activation) from year 1 to the visit preceding the event.

Abbreviations: CXCL10, interferon inducible protein 10; IL-6, interleukin 6; IQR, interquartile range; sTNFR, soluble tumor necrosis factor receptor.

M.M. Lederman 2018;218:239–48

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

A total of 4685 patients were followed for a mean of 3.0 years.

Treatment-naive pts with CD4+ count > 500 cells/mm³ (N = 4685)

→ **Immediate ART** (n = 2326)

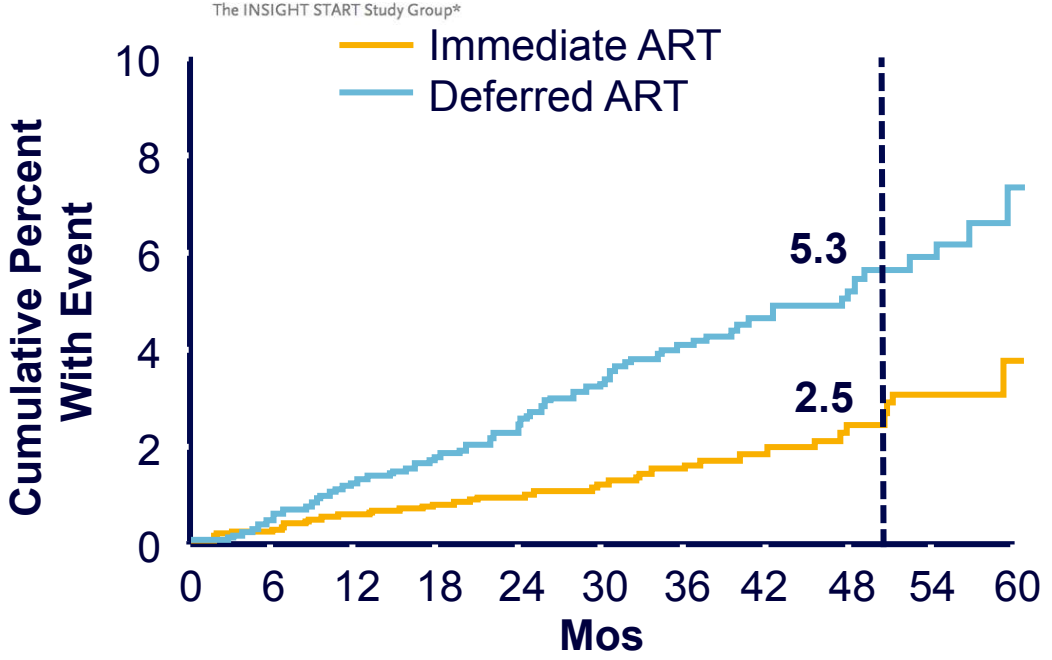
→ **Delayed ART (until CD4+ ≤ 350 cells/mm³) (n = 2359)**

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

START: Primary Outcome

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

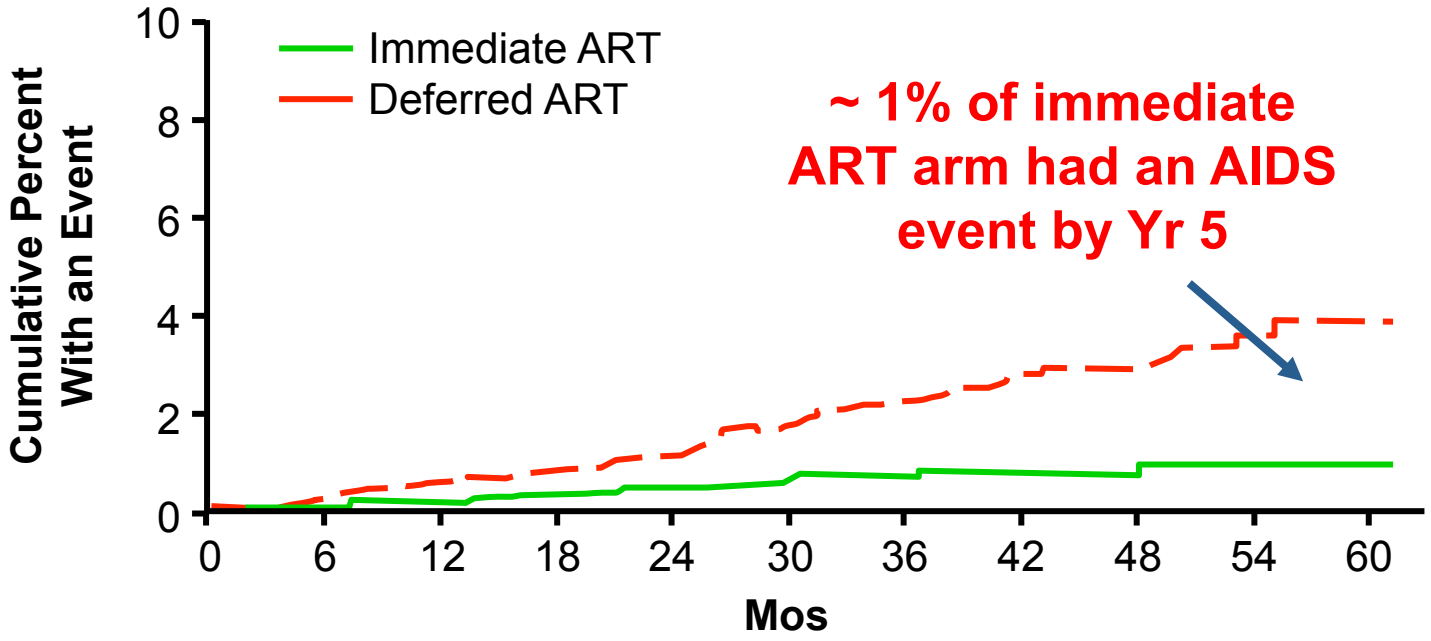


- **57% reduced risk of serious events or death with immediate ART**
- 68% of primary endpoints occurred in pts with CD4+ cell counts > 500 cells/mm^3

Primary Endpoint	Immediate ART	Deferred ART
No. with event (%)	42 (1.8)	96 (4.1)
Rate/100 PY	0.60	1.38
HR (immediate/deferred)	0.43 (95% CI: 0.30-0.62; *P* < .001)	

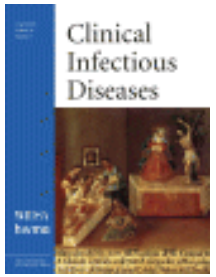
INSIGHT START Group. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

START: Reduced but Persistently High Risk of AIDS Event With Early ART



- 72% reduced risk of serious AIDS events with immediate ART

INSIGHT START Study Group. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

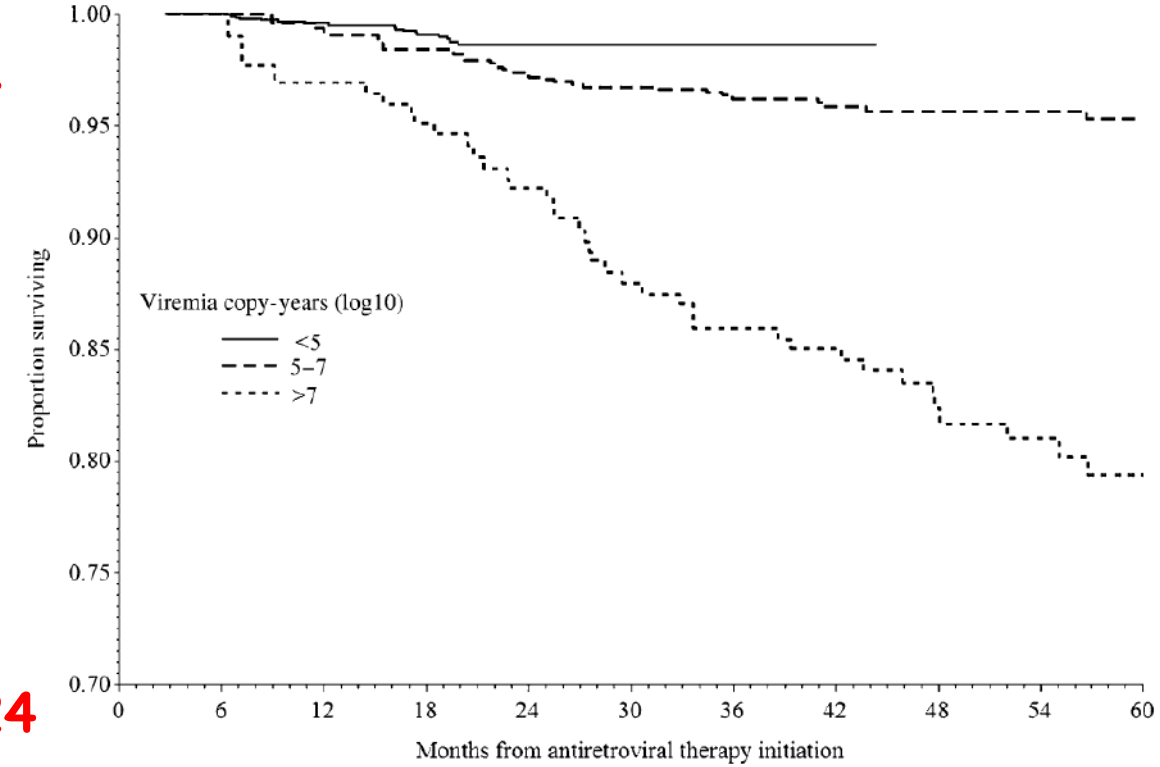


Viremia Copy-Years Predicts Mortality Among Treatment-Naive HIV-Infected Patients Initiating Antiretroviral Therapy

Mugavero M.J.
2011;53(9):927–935

Cumulative plasma HIV burden, demonstrated prognostic value for all-cause mortality among 2027 HIV-infected patients following ART

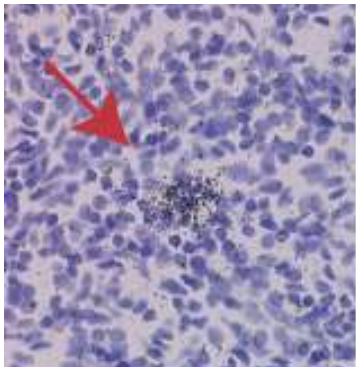
(viral load values prior to 24 weeks of ART initiation were excluded)



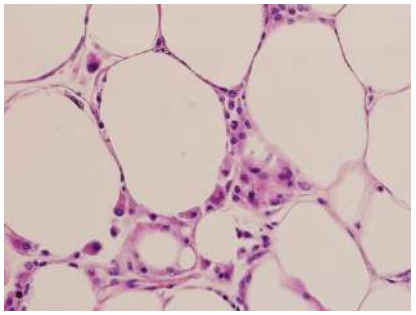
Viremia copy-years (log_{10})	Number at risk									
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
<5	1692	1414	1105	317	79	18	2			
5–7	245	289	332	833	851	727	606	509	414	316
>7	90	135	181	192	183	169	152	132	122	108

Attenzione…

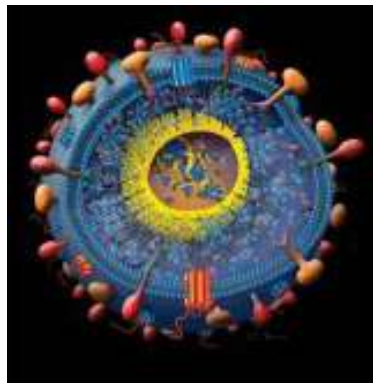
HIV production
HIV replication



HIV-associated fat
Metabolic syndrome

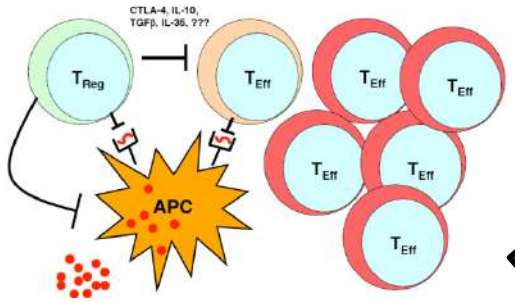


CMV- HCV
Excess pathogens

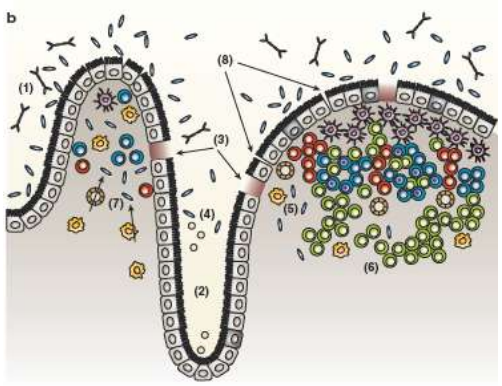


Inflammation
↑ Endothelium adhesion
↑ Monocyte activation
Dyslipidemia
Hypercoagulation/
thrombotic events
Endothelial dysfunction

Increased incidence of comorbidities and clinical disease



HIV-mediated loss of regulatory cells (Tregs)



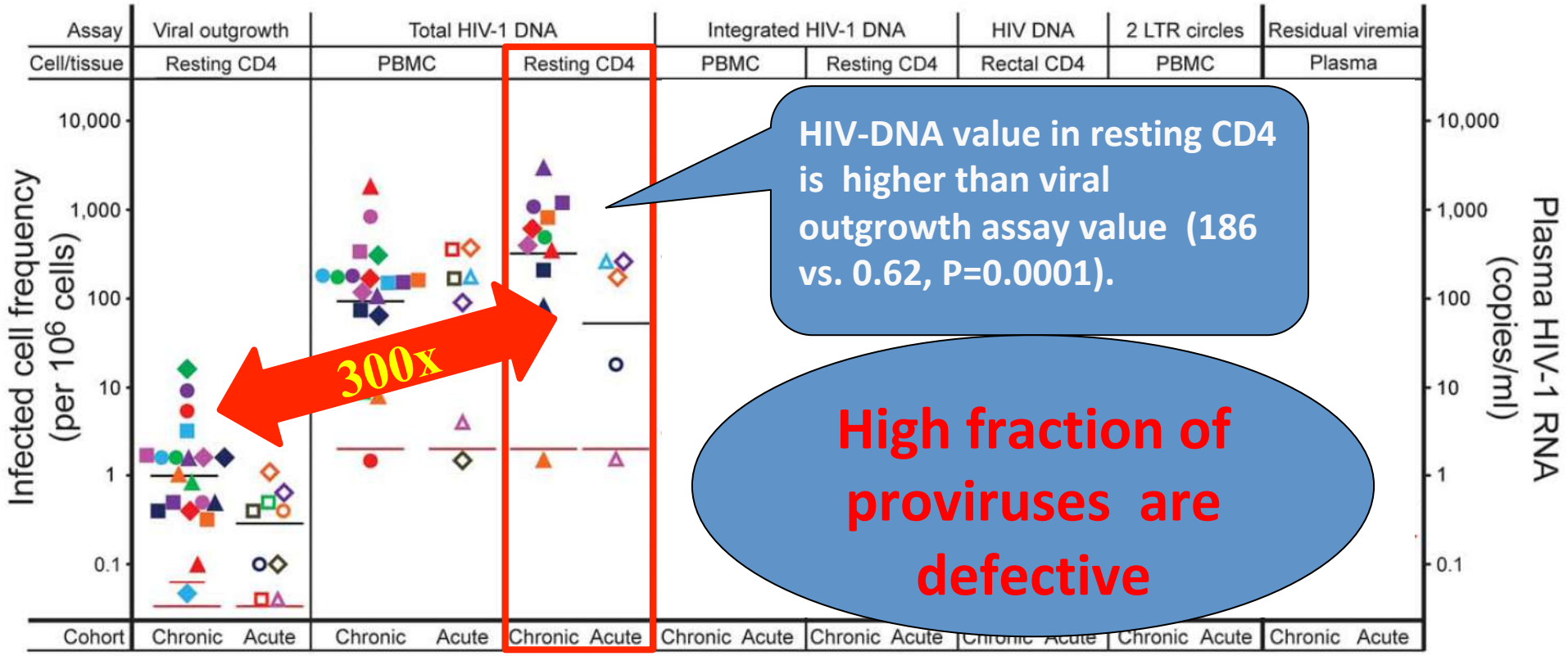
Microbial translocation

OPEN ACCESS Freely available online

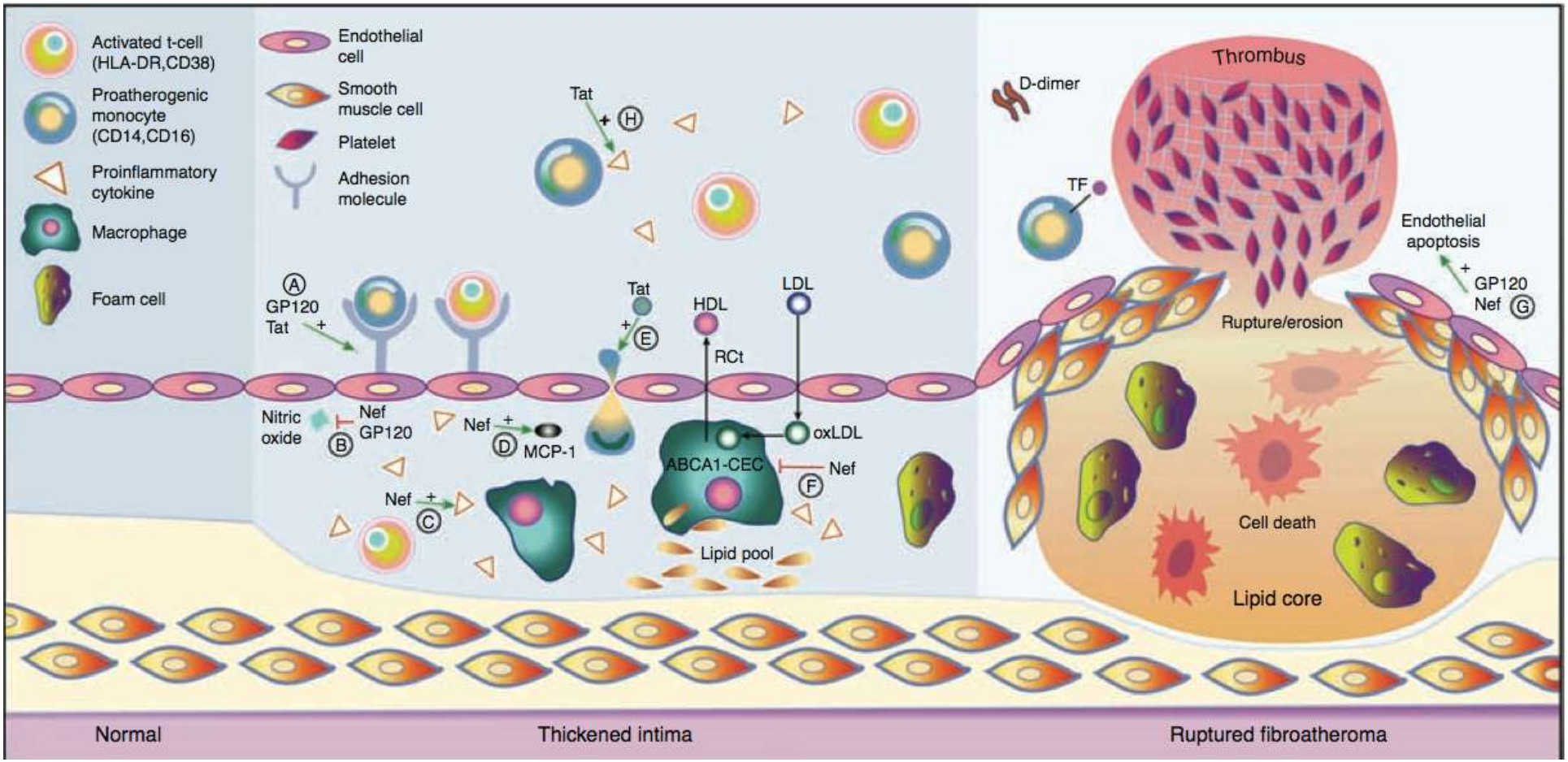
PLOS | PATHOGENS

Comparative Analysis of Measures of Viral Reservoirs in HIV-1 Eradication Studies

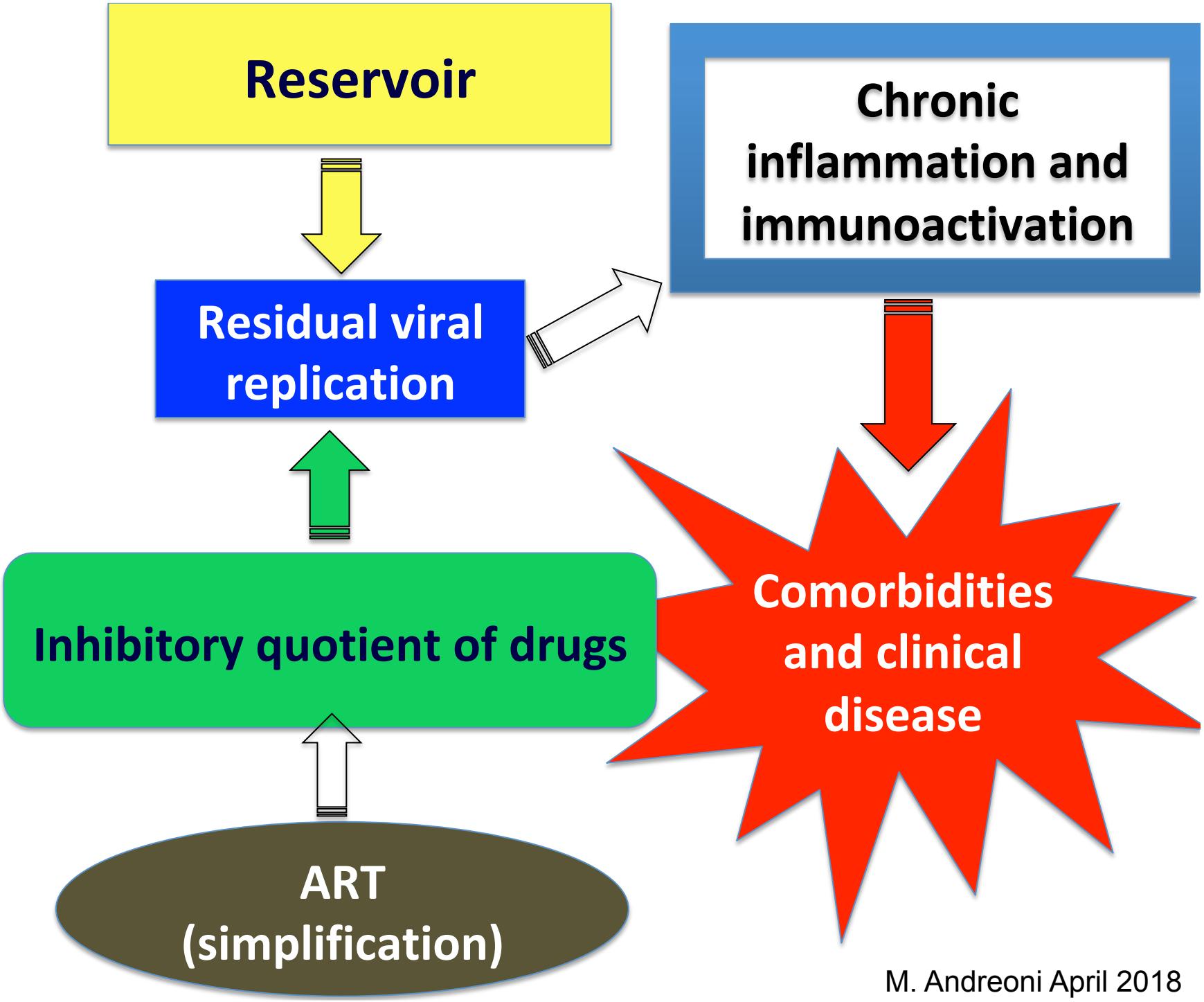
Susanne Eriksson[1☯], Erin H. Graf[2☯], Viktor Dahl[1☯], Matthew C. Strain[3☯], Steven A. Yukl[4,5☯], Elena S. Lysenko[2], Ronald J. Bosch[6], Jun Lai[7], Stanley Chioma[7], Fatemeh Emad[7], Mohamed Abdel-Mohsen[5], Rebecca Hoh[5], Frederick Hecht[5], Peter Hunt[5], Ma Somsouk[5], Joseph Wong[4,5], Rowena Johnston[8], Robert F. Siliciano[7,9], Douglas D. Richman[3], Una O'Doherty[2], Sarah Palmer[1], Steven G. Deeks[5], Janet D. Siliciano[7]*



Effects of HIV viral proteins on the development of atherosclerosis

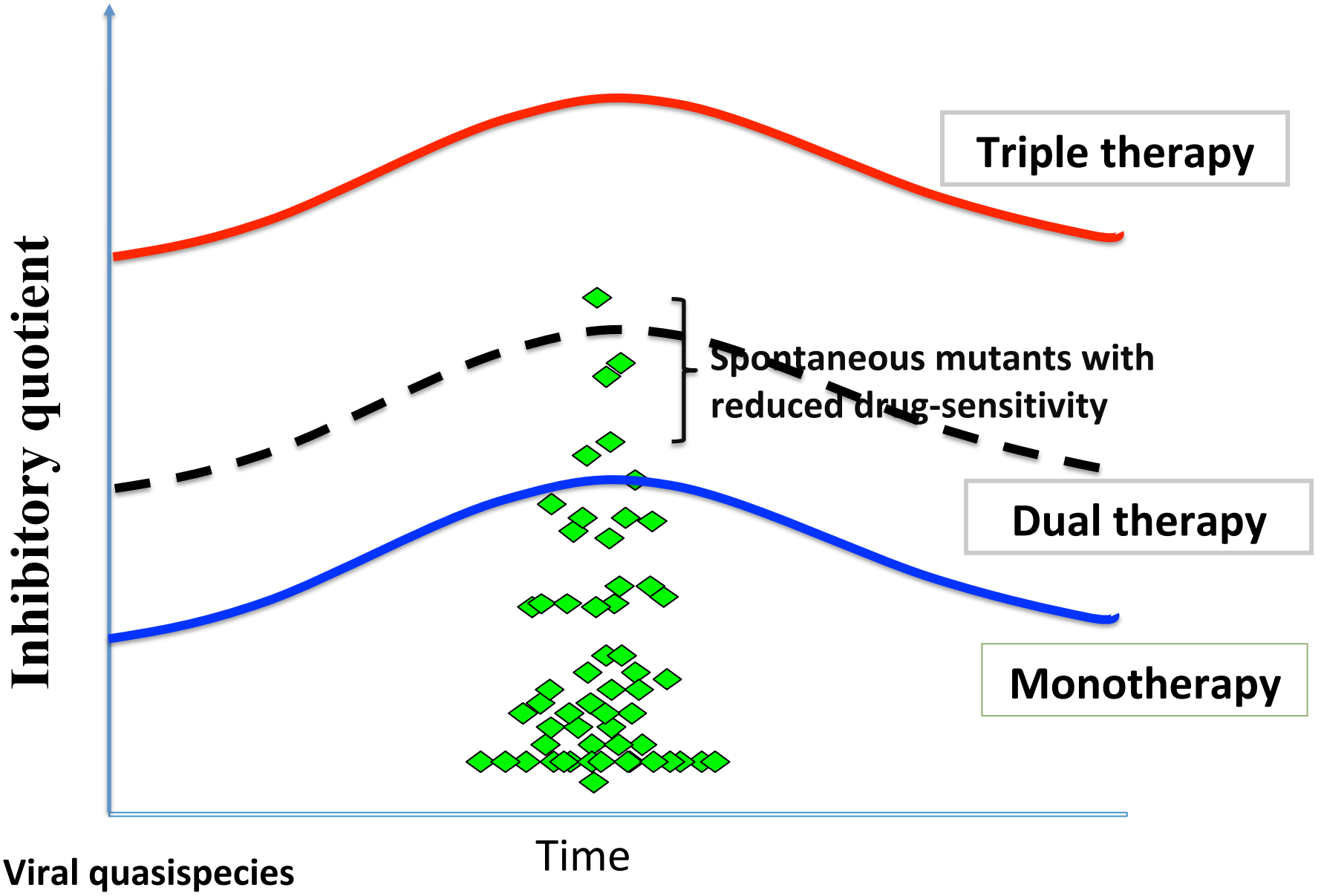


E. Nou AIDS 2016, Vol 30 No 10



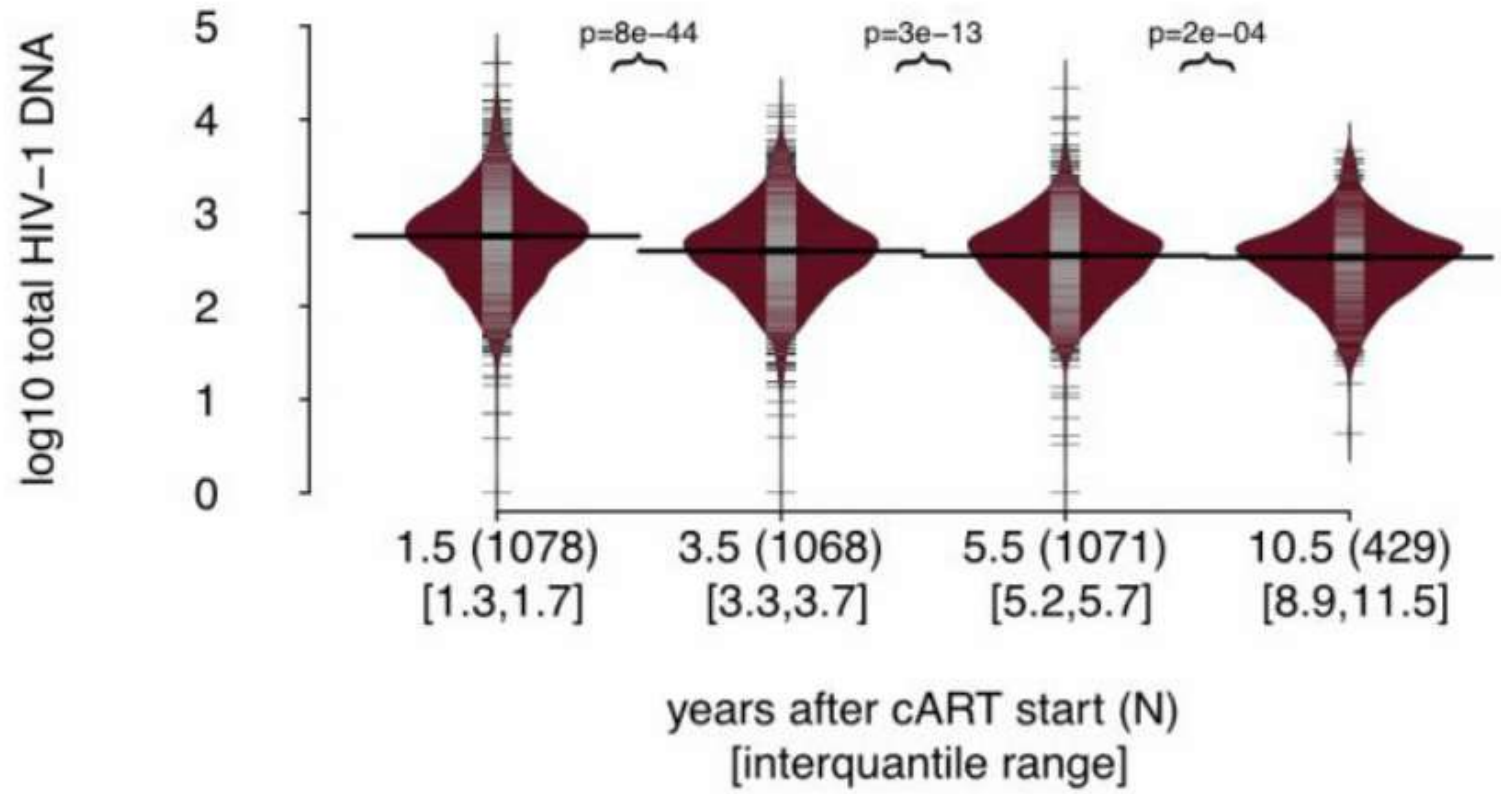
M. Andreoni April 2018

Dual Therapy: reaching clinical evidence



Dynamics of the HIV reservoir during suppressive ART

Blood HIV1 DNA decay slower and slower over time but still significant after 10 ART years



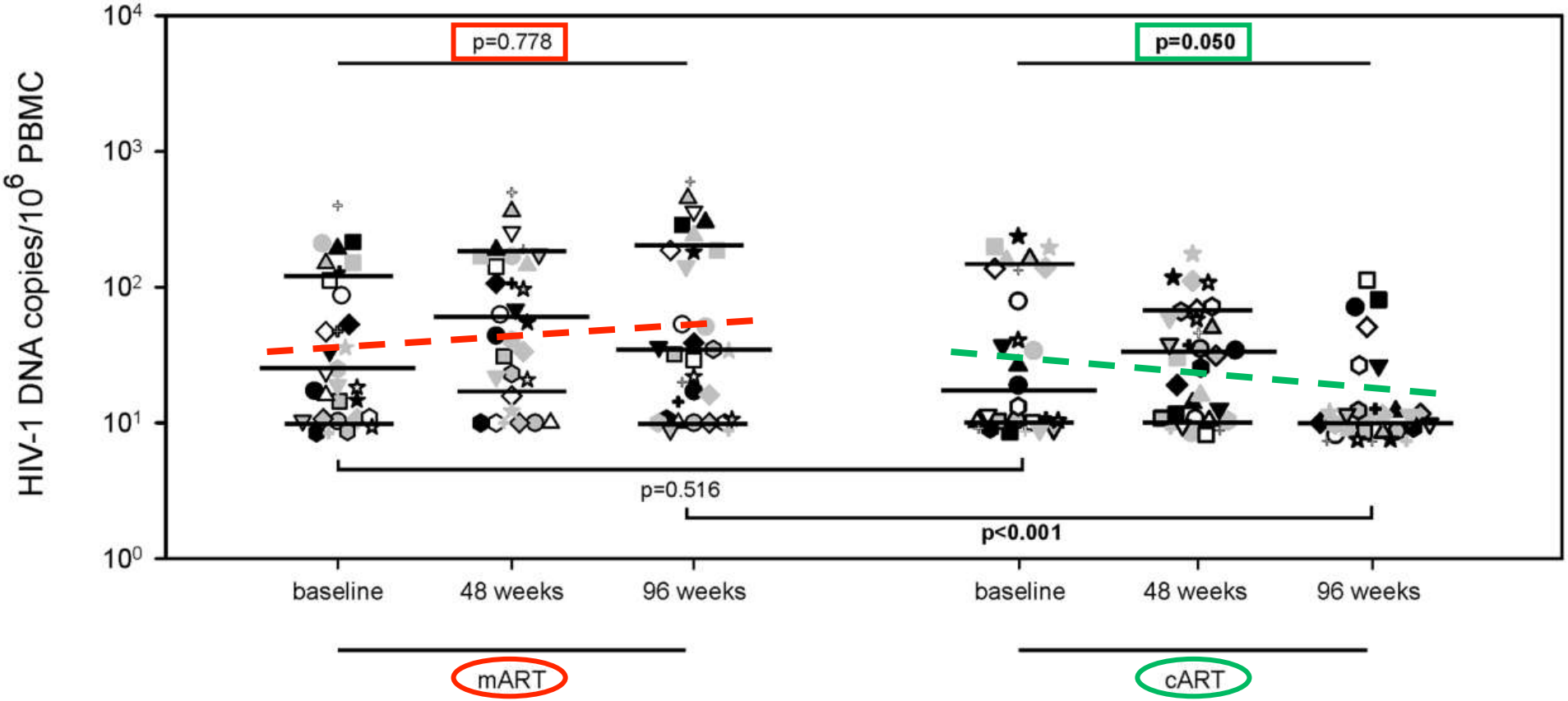
Short lines: Individual observations
Long black lines: Median

Red beans: Density of distributions
P-values: By paired Wilcoxon test

Bachmann, CROI 2018

Is reduced drug pressure impairing the dacay of HIV reservoir?

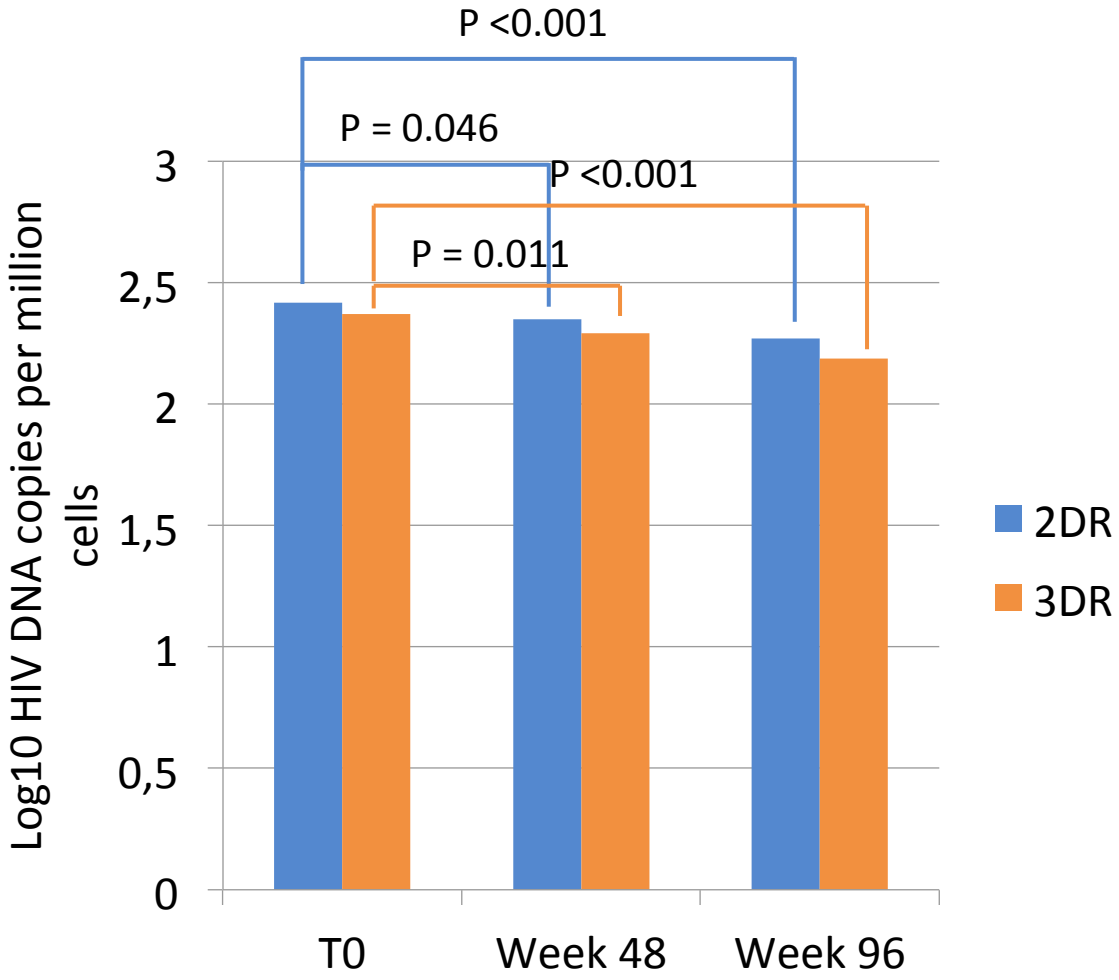
32 virosuppressed patients who switched to mono-LPV (mART) vs. 32 matched patients who continued cART



- There were 3 vs. 0 virological failures in mART vs. cART
- mART also less favorable than cART in terms of intracellular HIV RNA, B and T cell activation, microbial translocation, EBV DNA levels

Petrara, PLoS ONE 2017

Is reduced drug pressure impairing the dacay of HIV reservoir?



- Subset of 201 of 266 randomized patients
  - 104 in the dual-therapy (2DR) arm
  - 97 in the triple-therapy (3DR) arm
- Median years from HIV diagnosis
  - 3.8 2DR
  - 4.4 3DR
- Median years from first ART
  - 3.0 2DR
  - 2.4 3DR

ATLAS-M Study – Lombardi, JAC 2017; Fabbiani, JAC 2018

Cumulative Antiretroviral Exposure Measured in Hair Is Not Associated With Measures of HIV Persistence or Inflammation Among Individuals on Suppressive ART

DK McMahon 2018;218:234–8

No significant correlation between hair concentrations ARVs and measures of HIV persistence (plasma HIV-1 RNA by single copy assay, cell-associated-DNA, cell-associated RNA)

or soluble markers of inflammation.

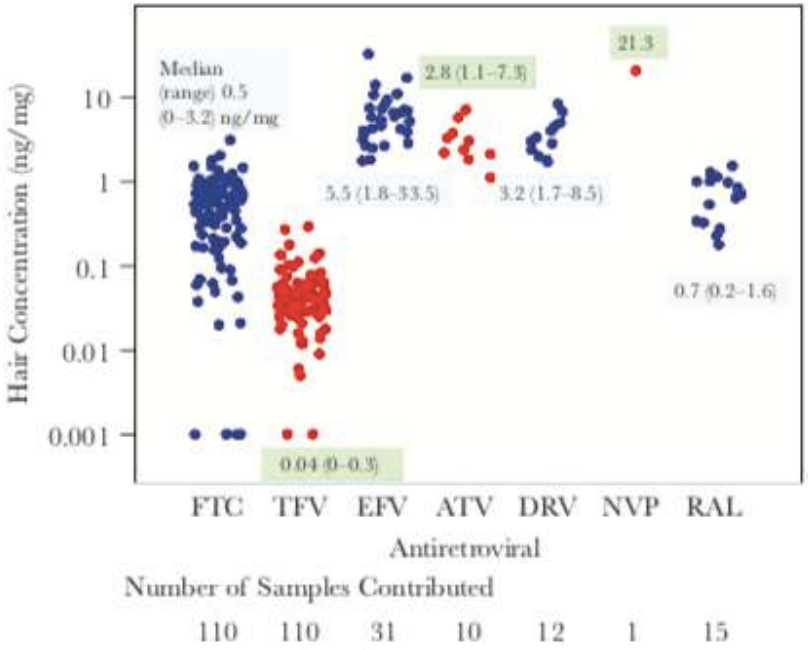
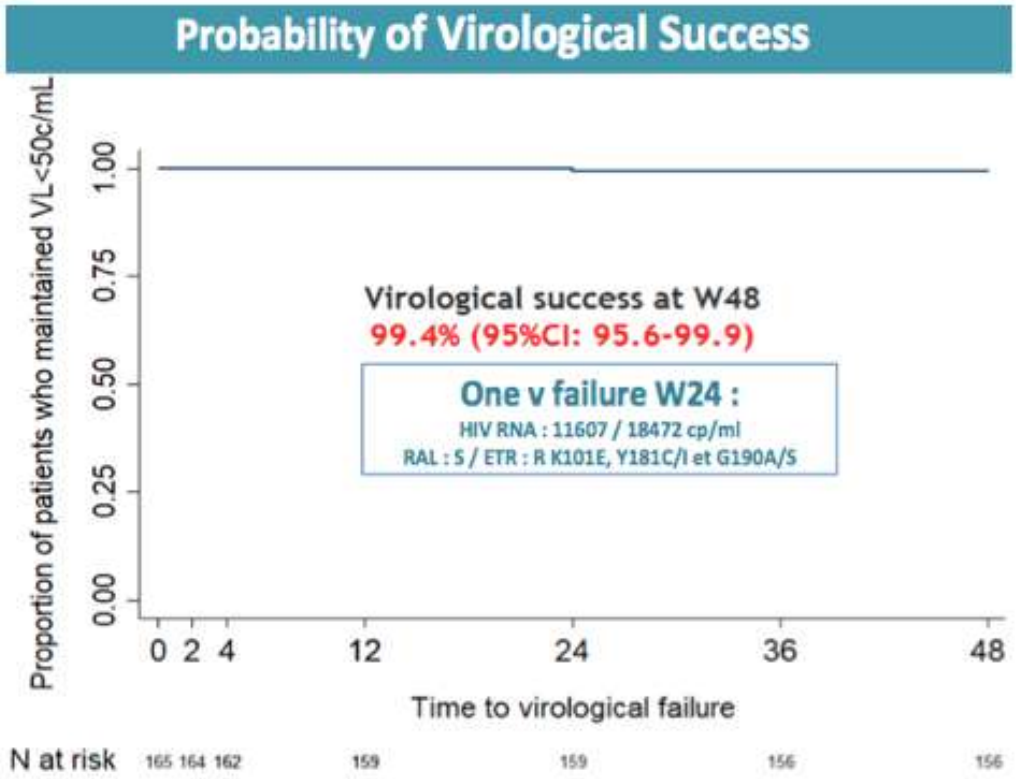


Table 1. Demographics of Participants in the A5321 Hair Study (n = 110)

Participant Characteristic	N or Median (%, range or IQR)
Age at study entry (years)	48 (range 23–69)
Sex	
Male	84 (76%)
Female	26 (24%)
Race/ethnicity	
White non-Hispanic	65 (59%)
Black non-Hispanic	17 (15%)
Hispanic	25 (23%)
Asian/Pacific Islander	3 (3%)
Years of ART at study entry	7 (range 4–16)
CD4⁺ cell count (cells/mm³)	
Pre-ART	250 (IQR, 101–359)
Study entry	661 (IQR, 494–839)
Pre-ART plasma HIV-1 RNA (log_{10}cps/mL)	4.6 (IQR, 4.2–5.1)
ART regimen at A5321 entry (all TDF-FTC based)	46 (42%) EFV; 7 (6%) RPV; 1 (1%) NVP; 11 (10%) ATV/r; 18 (16%) DRV/r; 5 (5%) EVG/cobi; 22 (20%) RAL
Measures of viral persistence	
Plasma HIV-1 RNA (iSCA, copies/mL)	52% < 0.4; 48% ≥ 0.4
Cell associated HIV-1 RNA (copies/10^6 CD4⁺ cells)	48 (IQR, 14–142)
Cell associated HIV-1 DNA (copies/10^6 CD4⁺ cells)	564 (IQR, 229–1236)

Efficacy of a Maintenance Strategy **Raltegravir/ Etravirine** the ANRS 163 ETRAL trial

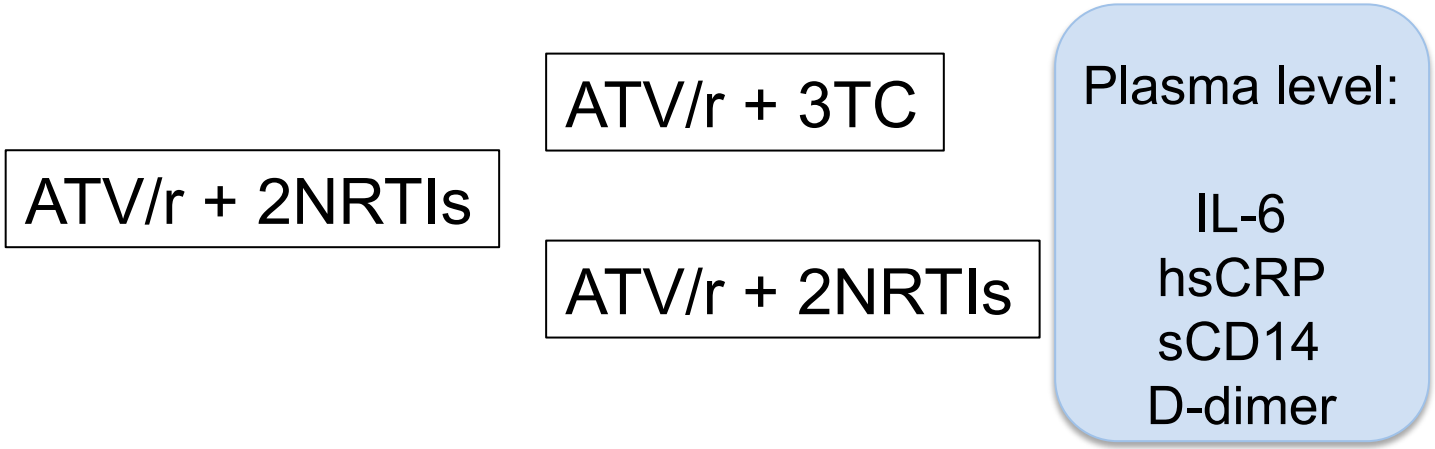
Pts: 165
Age: all > 45 years; HCV: 10%
all from b-PI regimens; duration of suppression: 6 yrs



Stable HIV DNA
CD4/CD8: 1.06 → 1.11

Katlama C et al. 9th IAS 2017. Abs MOPEB0314.

ATLAS-M: evolution of inflammation, monocyte activation and coagulation markers at week 48



Conclusion: We found no evidence of an impact of the simplification to a successful DT with ATV/r +3TC on markers of systemic inflammation as compared to continuing 3-drug therapy in patients with sustained virological suppression. Duration of infection is likely to drive the levels of inflammatory biomarkers in this setting. The long-term clinical consequences of these findings should be assessed.

Belmonti S et al. ICAR 2017; Poster 40

SWORD 1 and 2 studies

Inflammatory markers at week 48

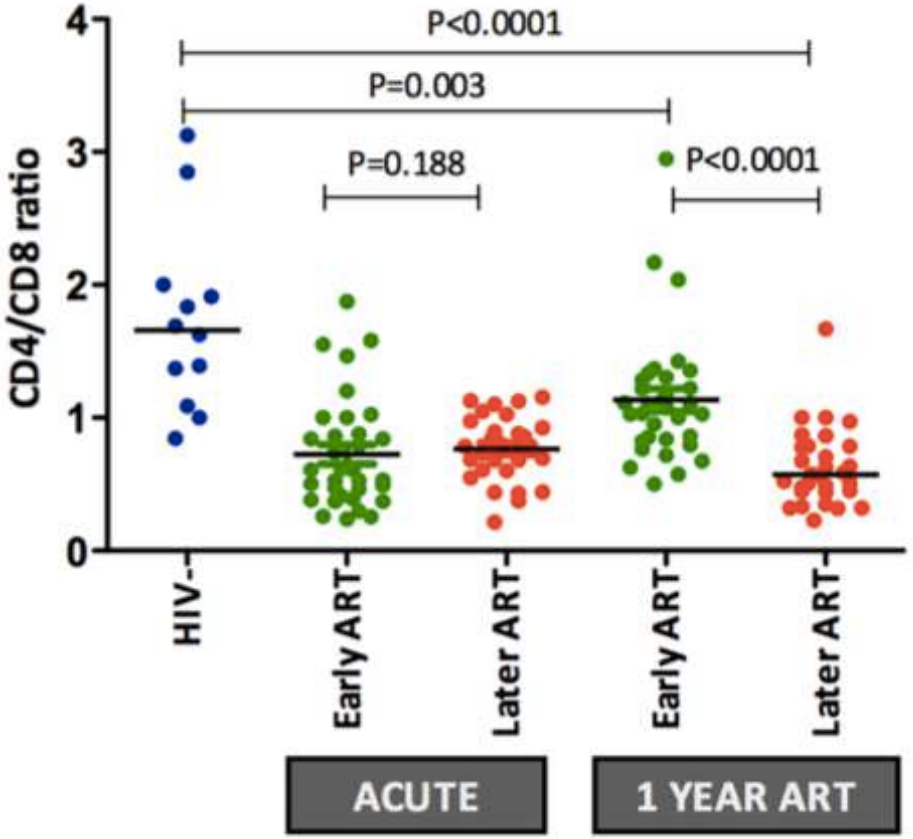
Biomarker	DTG + RPV n	DTG + RPV Mean (median [range])	CAR n	CAR Mean (median [range])	Week 48 difference, DTG+RPV − CAR (95% CI)
Inflammation					
C-RP, mg/L					
Baseline[a]	512	2.81 (1.3 [0.1, 34.4])	505	2.77 (1.3 [0.1, 33.8])	
Week 48	480	0.11 (0.0 [−32.7, 40.3])	482	0.47 (0.0 [−31.1, 96.0])	−0.36 (−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 [−3963.1, 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)

Neutral impact on markers of inflammation

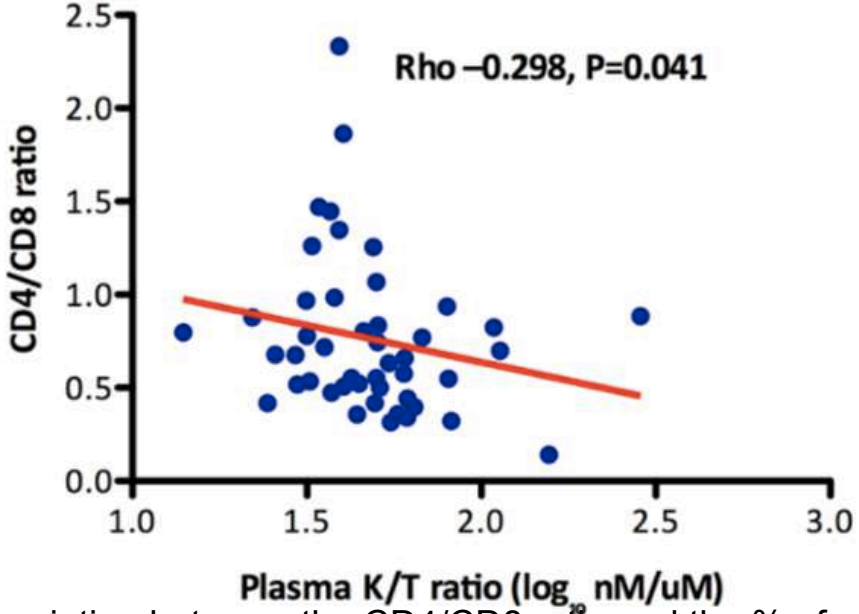
Orkin C et al. EACS 2017; BPD2/10

HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality

Impact of early or later ART initiation in CD4/CD8 ratio.



Increased innate and adaptive immune activation, an immunosenescent phenotype in pts with low CD4/CD8 ratio,



Association between the CD4/CD8 ratio and the % of CD282CD8+ T cells activity (kinurenine/tryptophan ratio)

Serrano-Villar S., PLOS Pathogens, May 2014 | Volume 10 | Issue 5

HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality

Serrano-Villar S., PLOS Pathogens, May 2014 | Volume 10 | Issue 5

CD4/CD8 ratio predicted increased risk of morbidity and mortality

	Beta	Std. error	P value
Madrid cohort (N = 66) (all subjects CD4≥500 cells/mm³)			
CD4+ T cells			
Unadjusted	−1.86	2.85	0.514
Adjusted by ART duration	−0.66	3.76	0.859
CD8+ T cells			
Unadjusted	2.80	1.12	0.013
Adjusted by ART duration	2.29	1.16	0.048
CD4/CD8 ratio			
Unadjusted	−6.23	2.48	0.012
Adjusted by ART duration	−5.08	2.53	0.045
SOCA cohort (N = 192)			
CD4+ T cells			
All subjects	−1.52	0.58	0.009
Subjects with CD4≥500 cells/mm³*	−4.09	6.43	0.525
CD8+ T cells			
All subjects*	0.28	0.33	0.392
Subjects with CD4≥500 cells/mm³*	2.37	2.05	0.246
CD4/CD8 ratio			
All subjects*	−1.38	0.55	0.012
Subjects with CD4≥500 cells/mm³*	−5.04	3.88	0.194

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

3,236 participants, 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.

Estimated probability of normalisation was

- ✓ by 1 year from baseline: 4.4% (95% CI 3.7–5.2),
- ✓ by 2 years: 11.5% (10.2–13.0),
- ✓ by 5 years: 29.4% (26.7–32.4) .

Factors associated with normalisation were high pre-ART CD4 cell counts, a high CD4/CD8 ratio at baseline, and negative cytomegalovirus serological findings.

Mussini C, Lancet February 6, 2015

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

The incidence rate of non-AIDS-defining events for patients with a CD4/CD8 ratio of

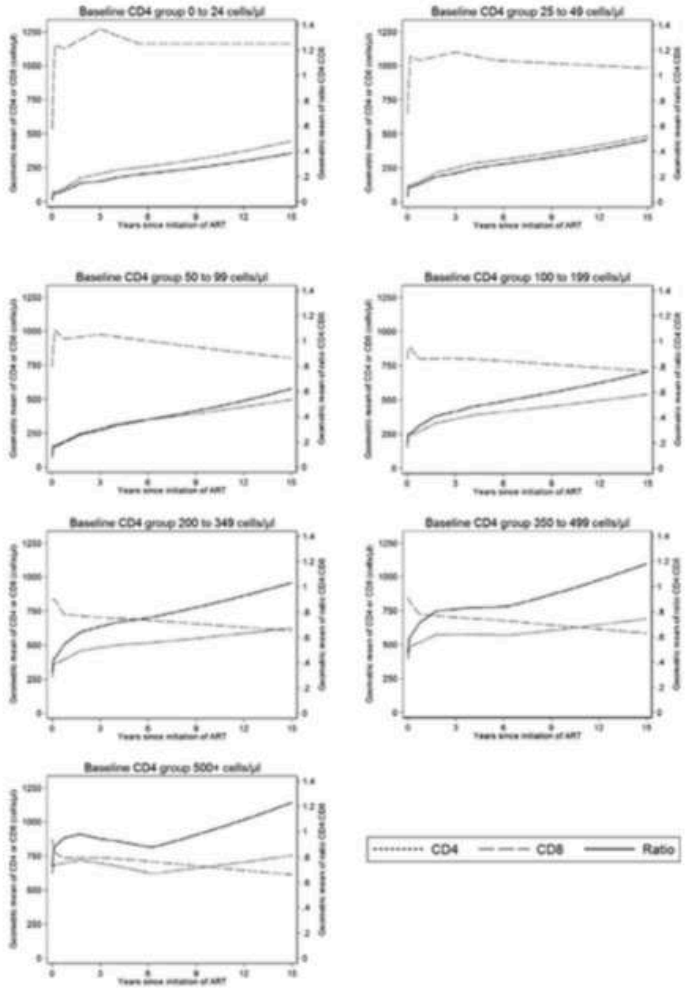
- ✓ <0.30: 4.2 per 100 pt/years, (95% CI 3.4–5.3)
- ✓ 0.30–0.45: 2.3 per 100 pt/years (95% CI 2.1–2.5)
- ✓ >0.45: 2.2 per 100 pt/year (95% CI 1.7–2.9).

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 C, Lancet February 6, 2015

Long terms trends in $CD4^+$ cell counts, $CD8^+$ cell counts, and the $CD4^+ : CD8^+$ ratio

RA Hughes, AIDS 2018, Vol 32 No 10



Number of participants followed (cumulative number of deaths) at 0, 3, 6, 9, 12 and 15 years post-ART

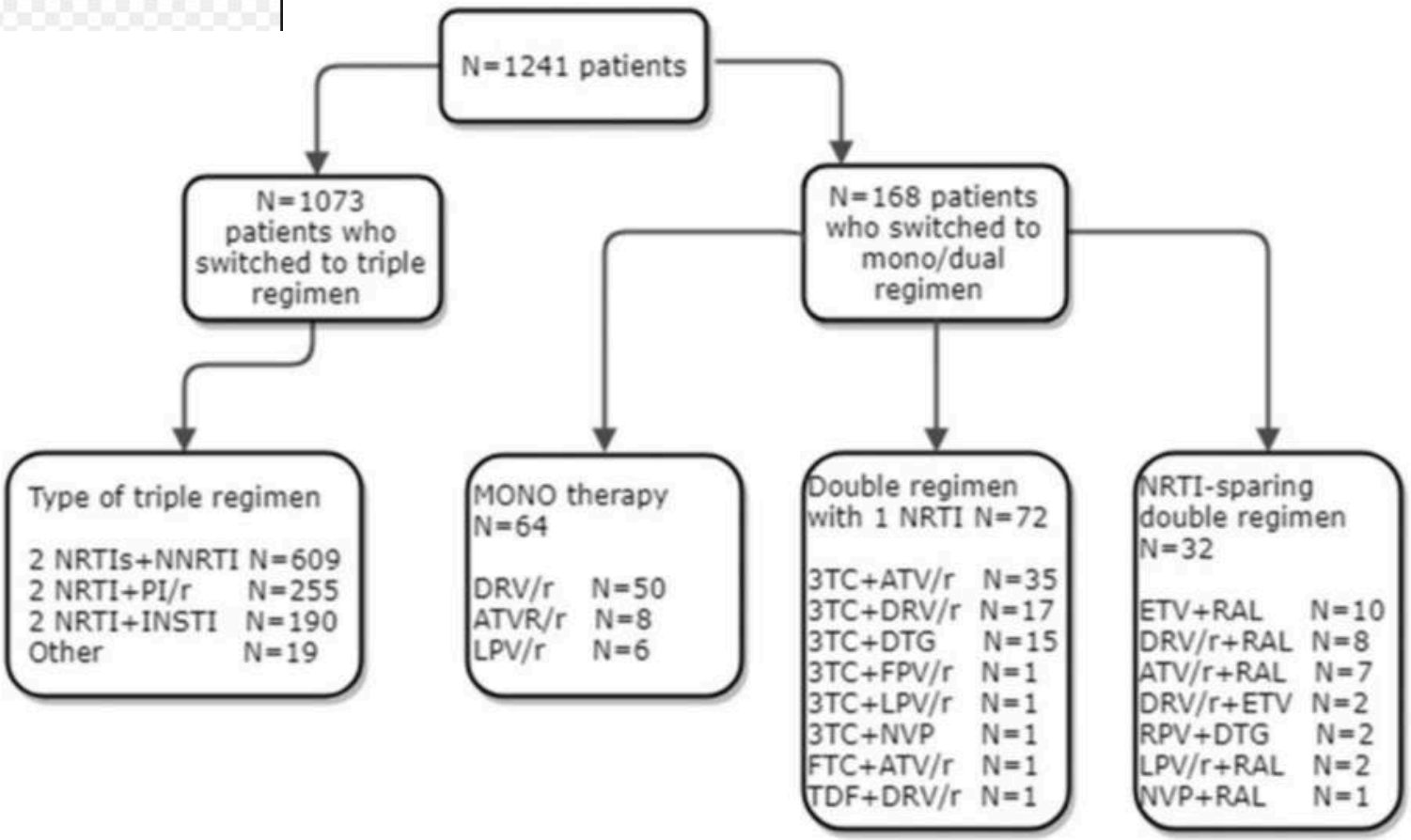
39,979 patients with a median follow-up of 53 months. Among patients with baseline CD4+ cell count >50 cells/ml, mean CD8+ cell counts continued to decrease between 3 and 15 years post-ART. During 15 years of follow-up, normalization of the predicted mean CD4+:CD8+ ratio (to >1) was only observed in patients with baseline CD4+ cell count > 200 cells/ml

Conclusion: Declines in CD8+ cell count and increases in CD4+ : CD8+ ratio occurred up to 15 years after starting ART.

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

BMC Medicine

Mussini et al. BMC Medicine (2018) 16:79



BMC Medicine

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

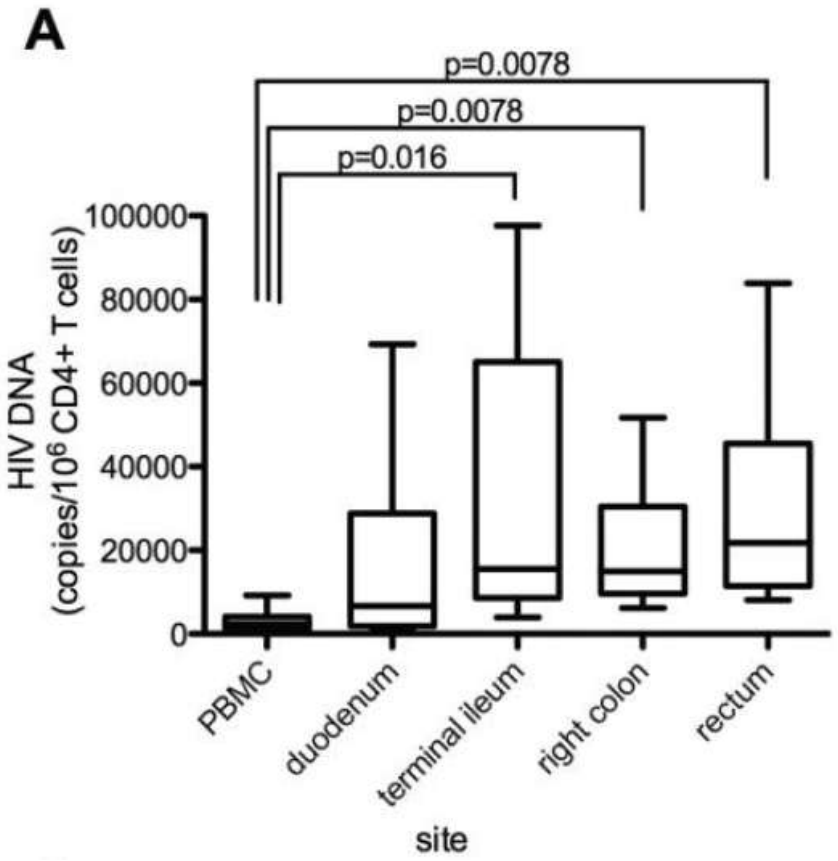
Mussini et al. 2018 16:79

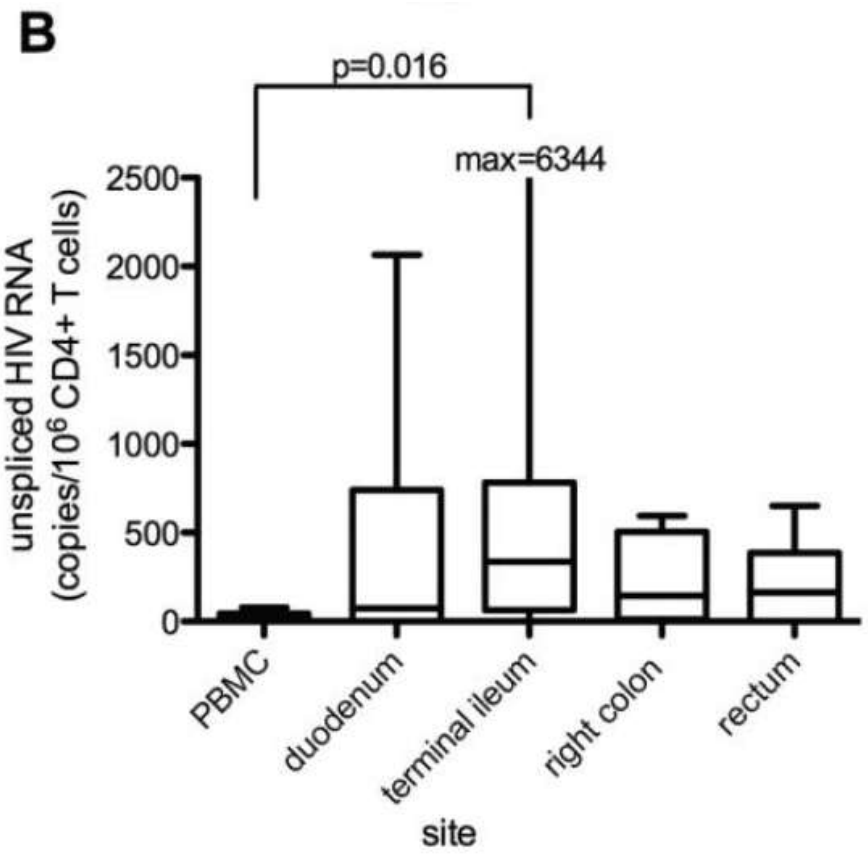
	Triple (*N* = 622)	Dual (*N* = 57)	*p* value
CD4/CD8 ratio			
At switch, mean (SD)	0.76 (0.45)	0.80 (0.37)	0.167
24 months after switch, mean (SD)	0.93 (0.71)	0.88 (0.43)	0.824
Change, mean (SD)	+0.17 (0.58)	+0.08 (0.19)	0.024
CD8 cell count			
At switch, mean (SD)	912 (458)	882 (471)	0.396
24 months after switch, mean (SD)	867 (451)	911 (411)	0.337
Change, mean (SD)	−45 (401)	+28 (256)	0.017
CD4 cell count			
At switch, mean (SD)	588 (285)	614 (269)	0.402
24 months after switch, mean (SD)	683 (294)	703 (272)	0.285
Change, mean (SD)	+95 (181)	+89 (175)	0.943

Patients switched to dual regimens showed a stabilization of the CD4/CD8 ratio, while patients in a three-drug-based regimen continued to improve the CD4/C8 ratio, for an increase in CD8 lymphocyte count in participants switching to dual therapy.

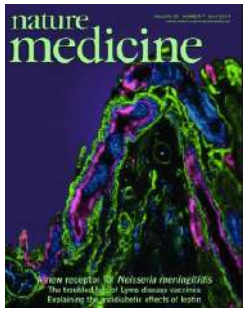
HIV reservoir = residual HIV infection

HIV DNA and RNA levels per CD4+ T cell were higher in all 4 gut sites compared with those in the blood.





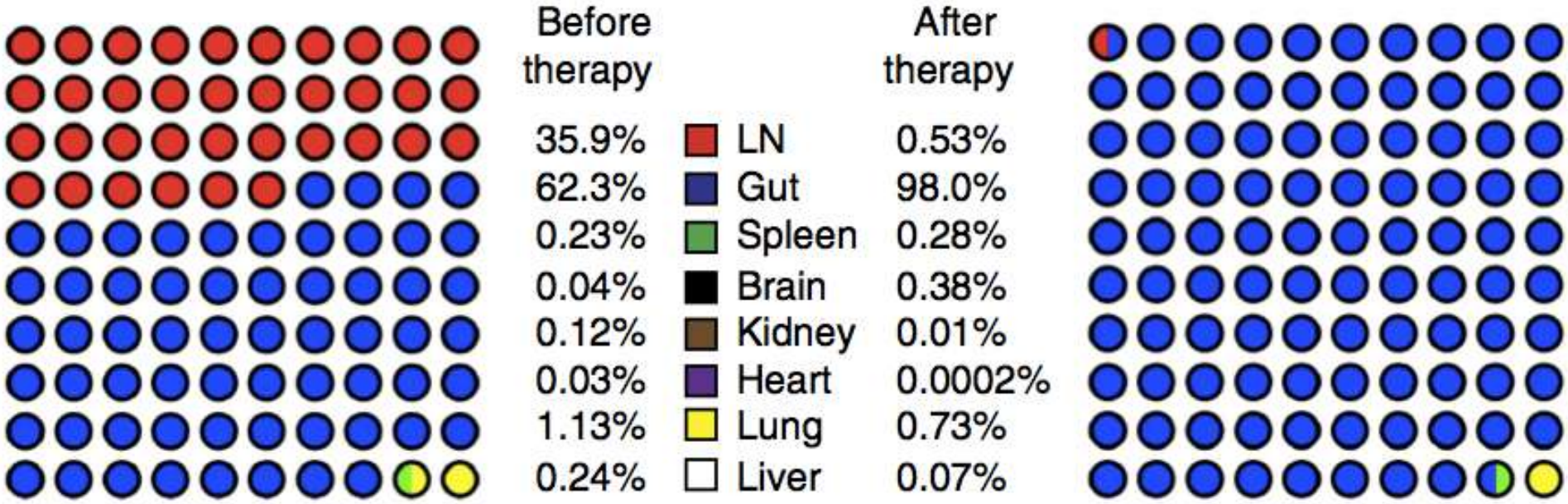
The Journal of Infectious Diseases 2010; 202(10):1553–1561



Defining total-body AIDS-virus burden with implications for curative strategies

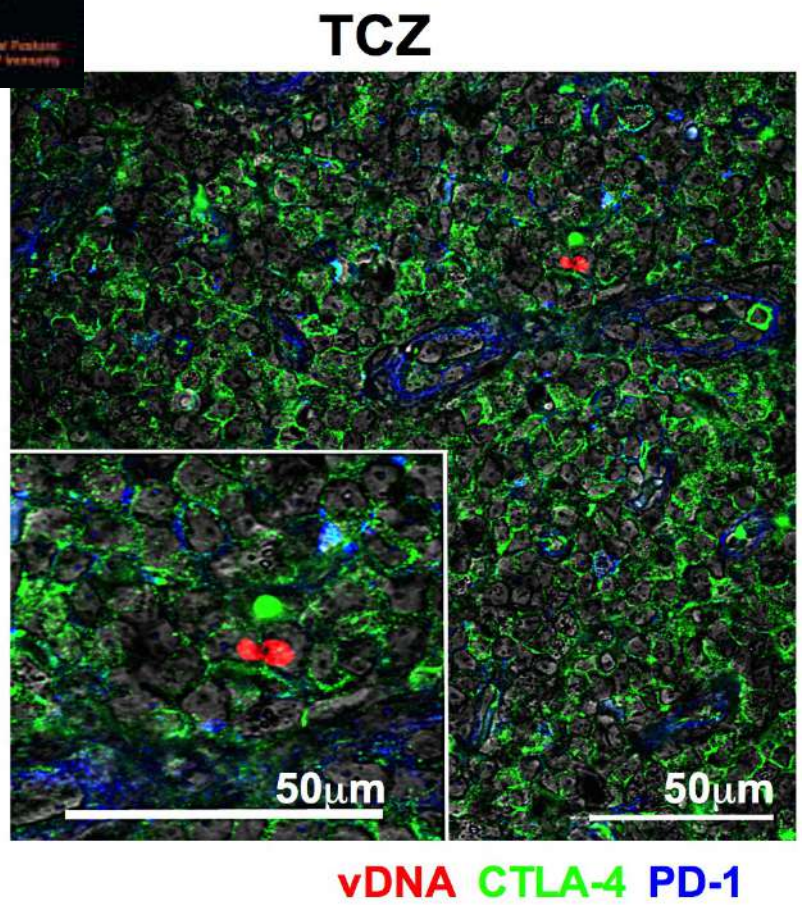
During ART the numbers of virus (v) RNA+ cells substantially decreased but remained detectable.

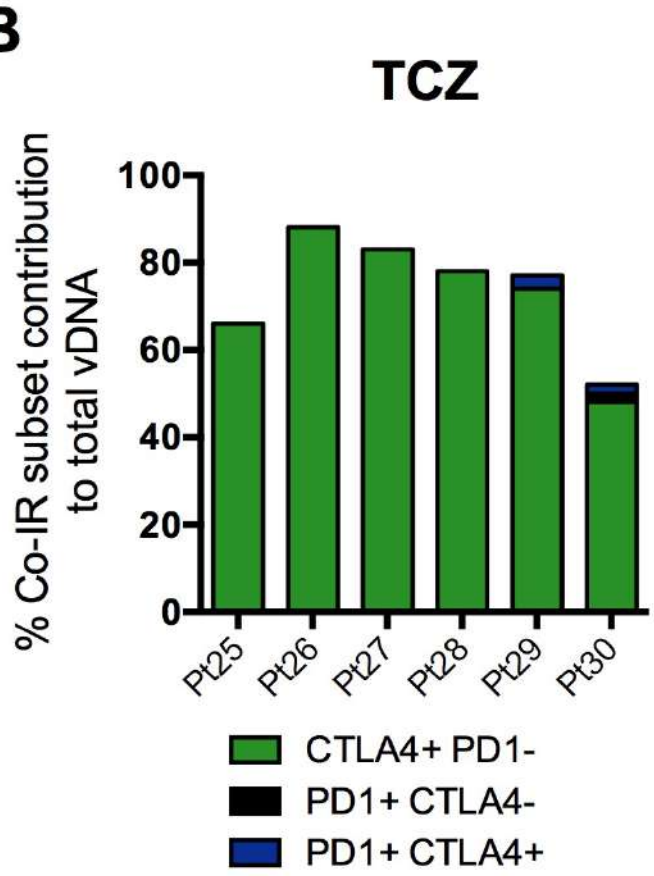
Graphical representation of the proportion of vRNA+ cells in each organ system before and during suppressive ART.



Jacob D Estes Nature Medicine 2017

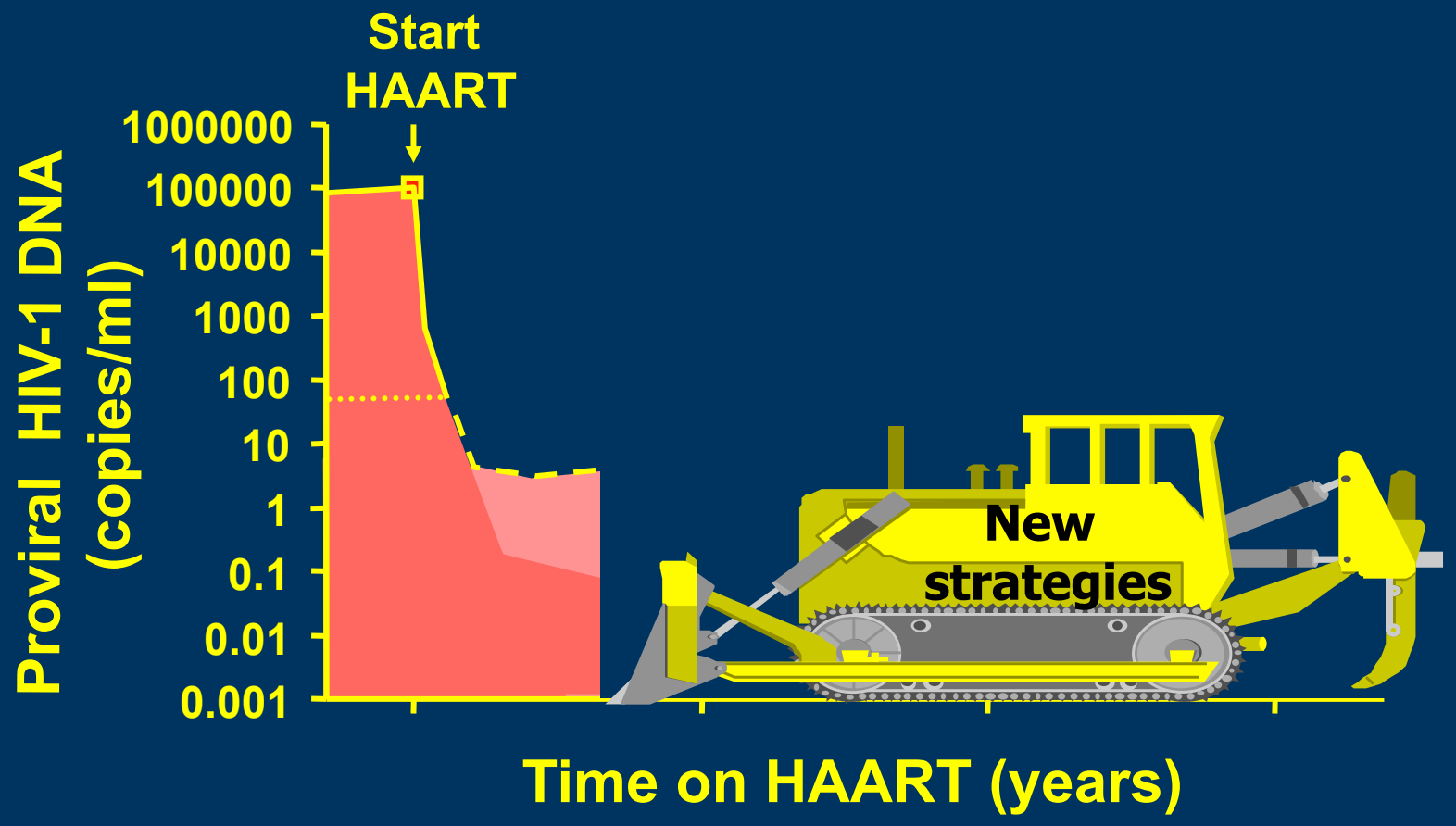
CTLA-4+PD-1- cells are the main contributor to HIV-DNA persistence in the TCZ of the LN



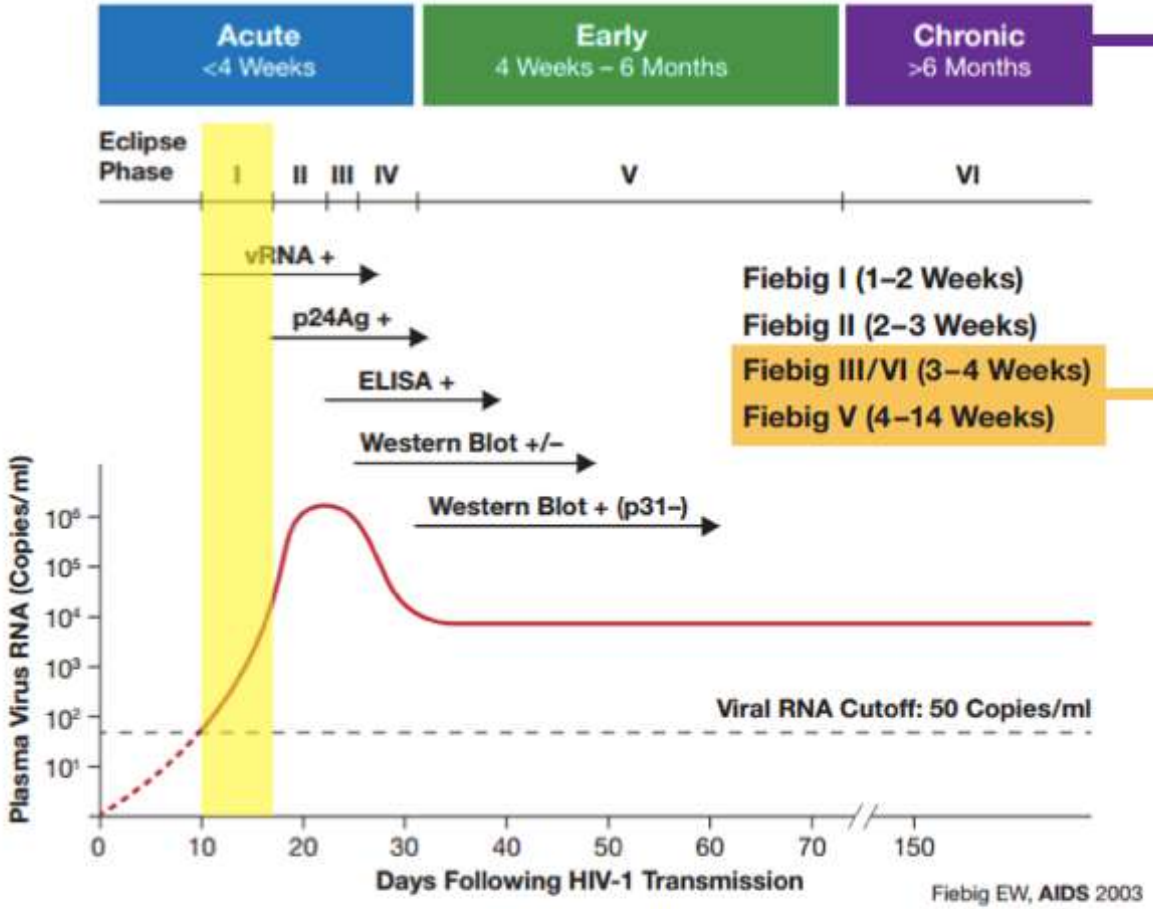


LN tissues from six HIV-infected individuals: on ART for 2-5 years, and undetectable viremia for >15 months

McGary et al., Immunity, 2017


Start
HAART
1000000
100000
10000
1000
100
10
1
0.1
0.01
0.001
Proviral HIV-1 DNA
(copies/ml)
New
strategies
Time on HAART (years)

Which impact of hyper acute treatment?



Median rebound 14 days

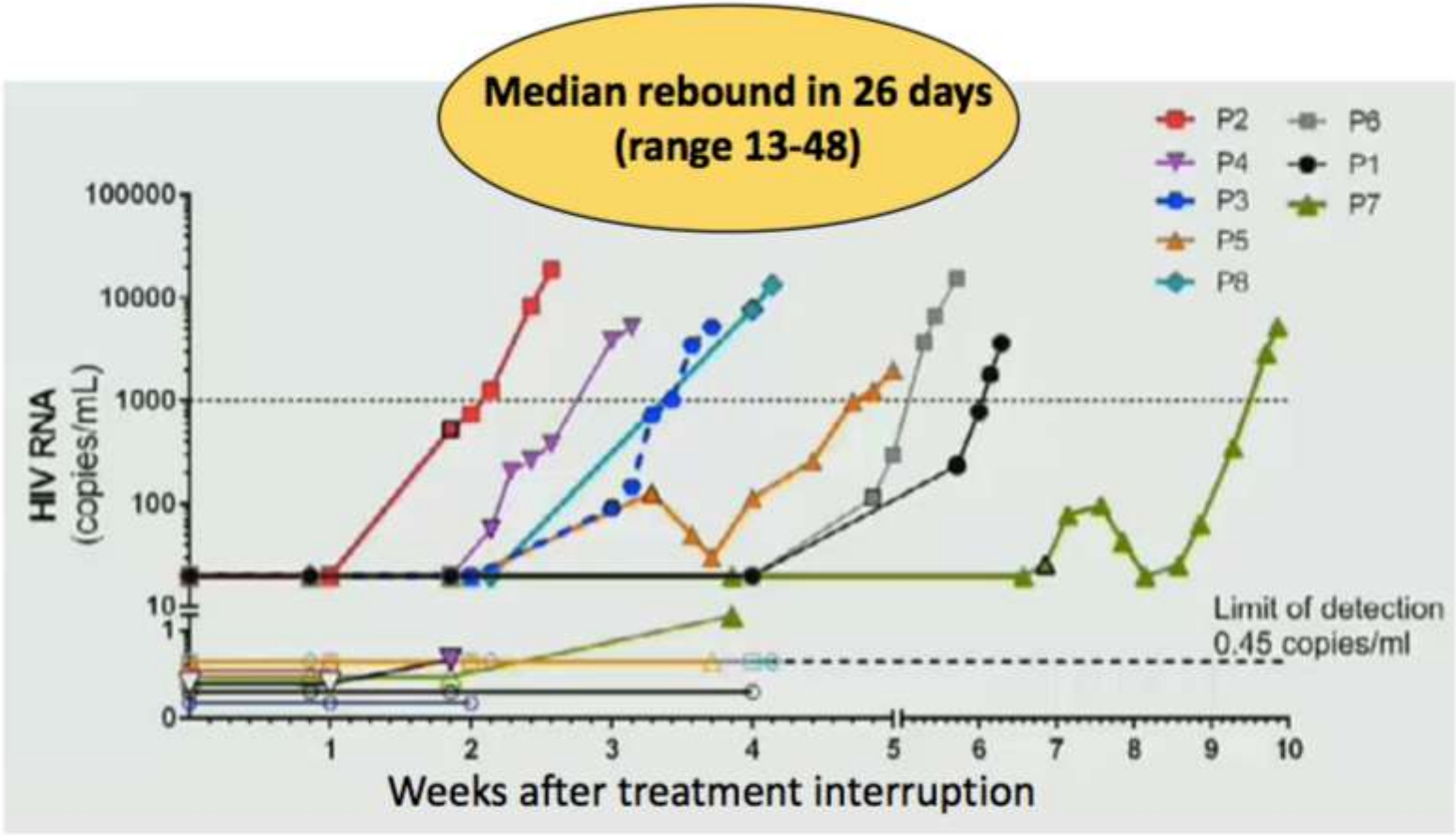
Median rebound 22 days

Study RV254 n=8 **participants treated during Fiebig I** for a median of 2.8 years

- HIV-DNA pre-ATI undetectable
- TILDA <1.4 tat/rev RNA+ cells/10^6 CD4 pre-ATI
- Pre-ATI, median CD4 was 561 cells/ul

Ananworanich J, CROI 2017

Hyper-acute treatment alone did not impact time to rebound



- CD4/CD8 ratio < 1 correlated with time to rebound
- HIV-specific CD8 increased post ATI and correlated with viral load

CD4 change post ATI -87 to 39 cells/μl
HIV-DNA levels >6 months went back to pre-ATII levels

Ananworanich J, CROI 2017

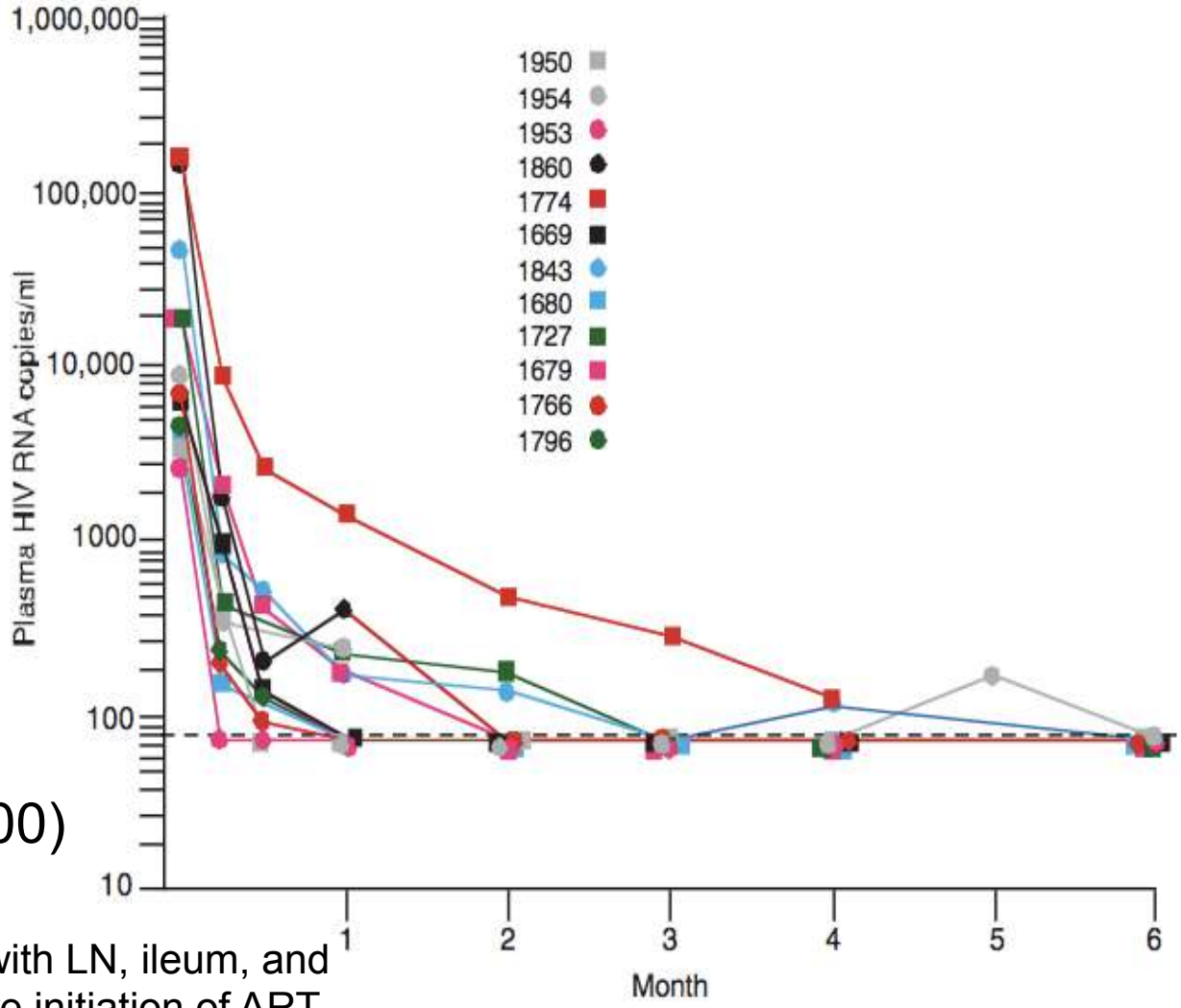
Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

12 Subjects received
TDF/FTC/EFV (n.6)
TDF/FTC/ATV/rtv (n.4)
TDF/FTC/DRV/rtv (n.2)

<u>At entry</u>

CD4: 467 μl (327-6220)

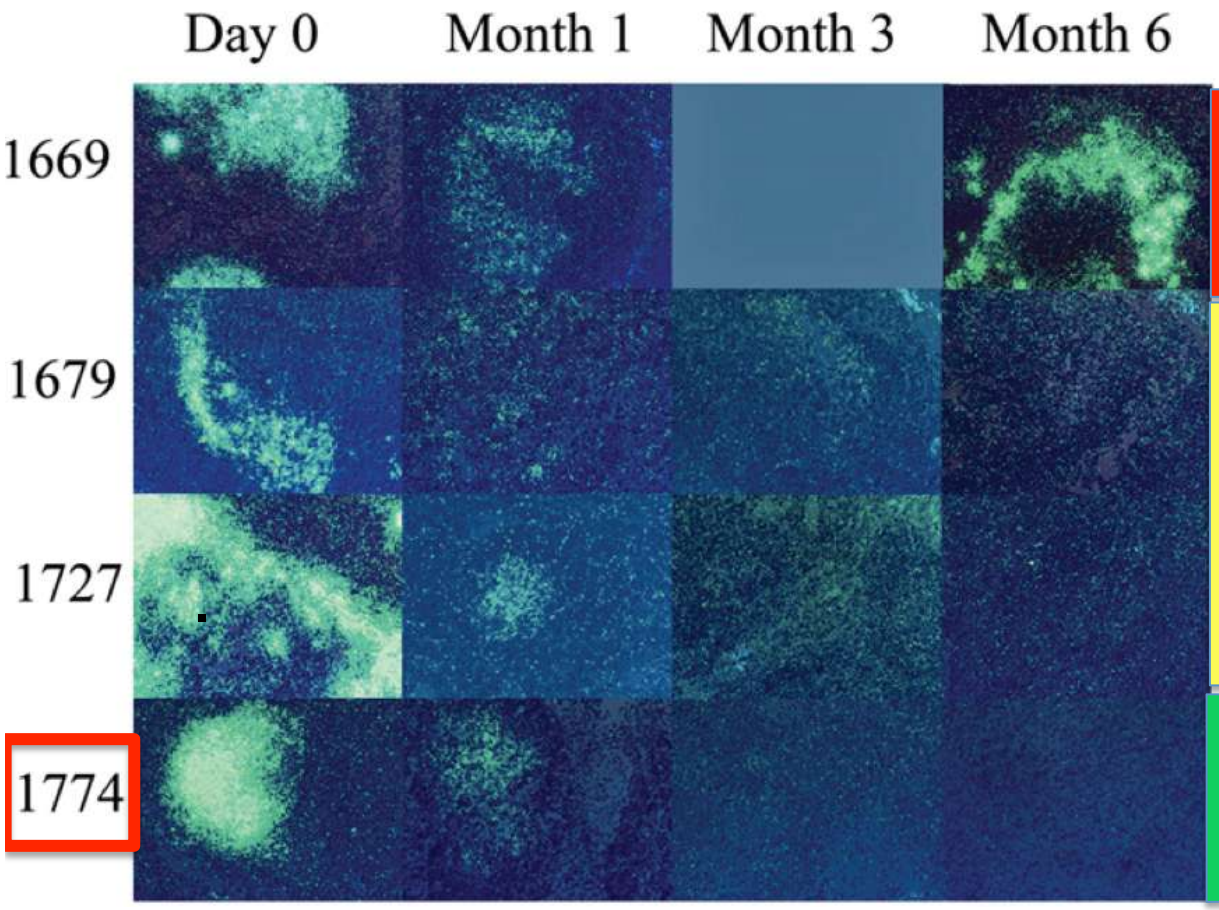
VL: 34,783 (2,530-157,000)



Subjects were followed for 6 mo with LN, ileum, and rectal biopsies obtained just before initiation of ART and again at months 1, 3, and 6.

C.V. Fletcher PNAS 11, 2014

Different rates of decay of HIV RNA from the FDCn of LN



No significant decrease

Initial decline and then decline more slowly at almost a flat rate

Continuous decay

FDCn: Follicular dendritic cell network

C.V. Fletcher PNAS 11, 2014

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

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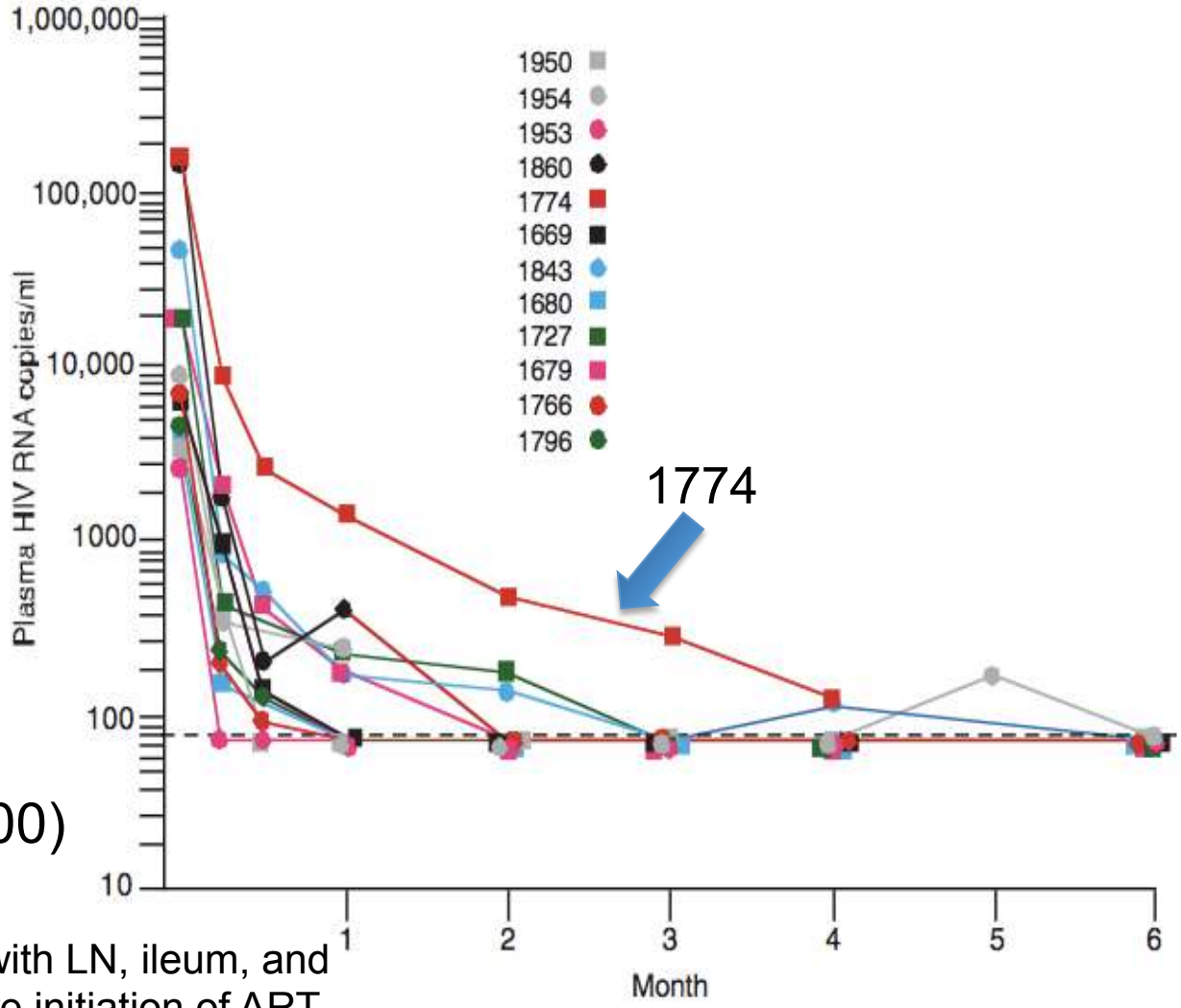
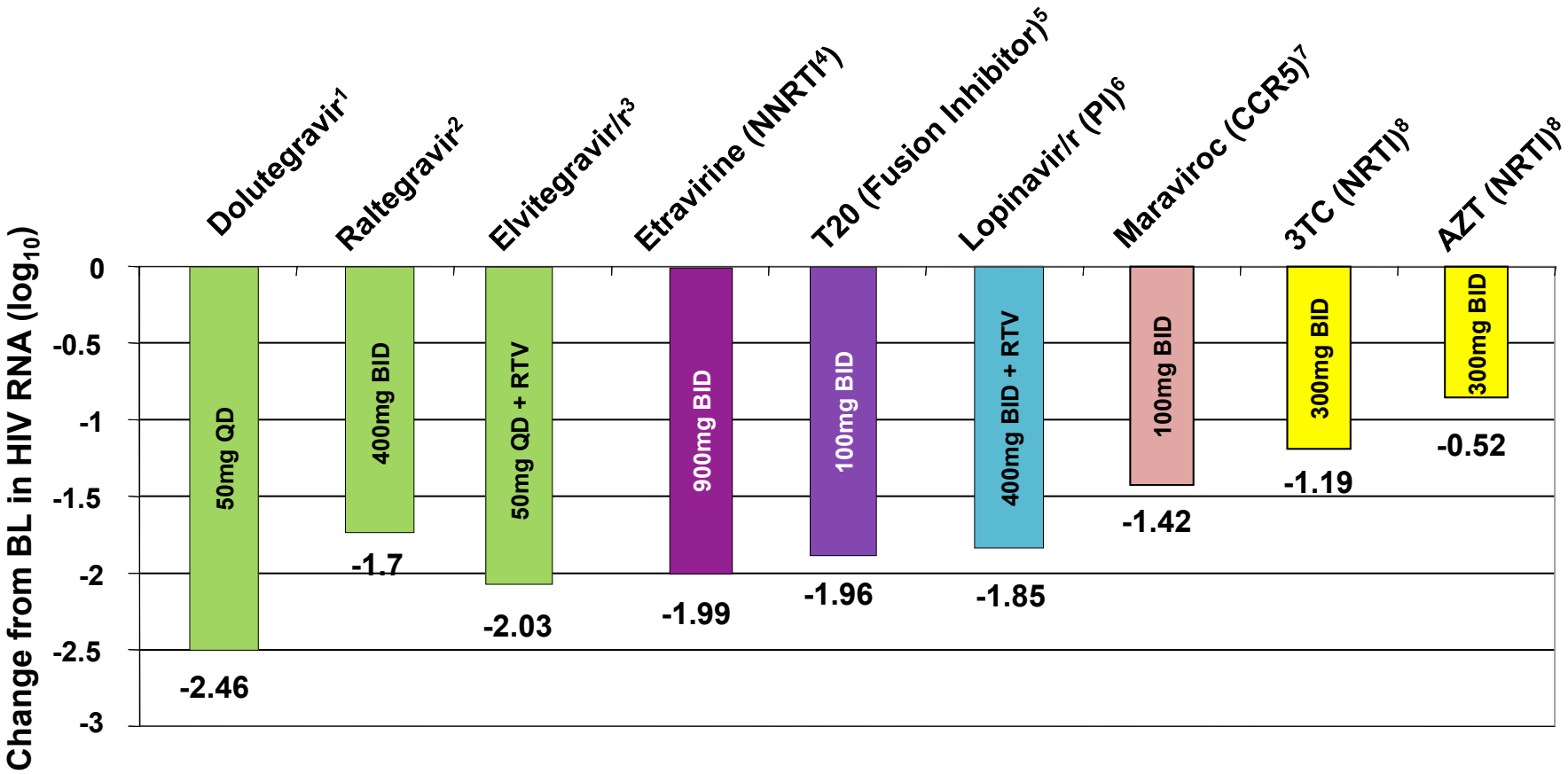


Subjects were followed for 6 mo with LN, ileum, and rectal biopsies obtained just before initiation of ART and again at months 1, 3, and 6.

C.V. Fletcher PNAS 11, 2014

Intrinsic potency of antiretrovirals

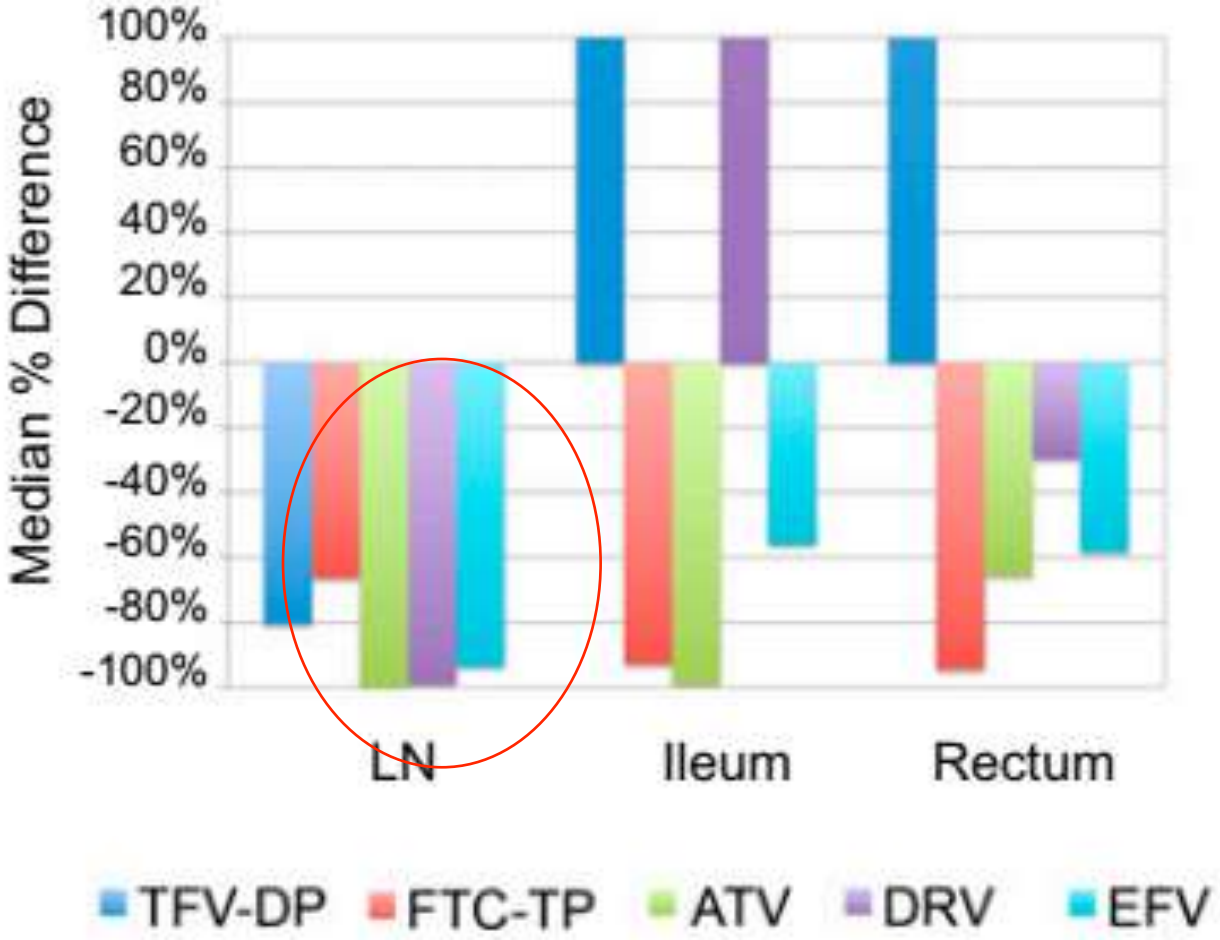


1. Lalezari J. 5th *IAS 2009*, *Cape Town,* abstract TUAB105.
2. DeJesus E. *J Acquir Immune Defic Syndr* 2006 ; 43:1-5.
3. Markowitz et al. *JAIDS* Volume 43(5) 15 December 2006 pp 509-515.
4. Sankatsing et al. *AIDS* 2003, 17:2623–2627.
5. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
6. Murphy RL. *AIDS* 2001;15:F1-F9.
7. Fätkenheuer G et al. *Nat Med* 2005 Nov; 11:1170-1172.
8. Eron JJ, *N Engl J Med* 1995, 333:1662-1669.

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

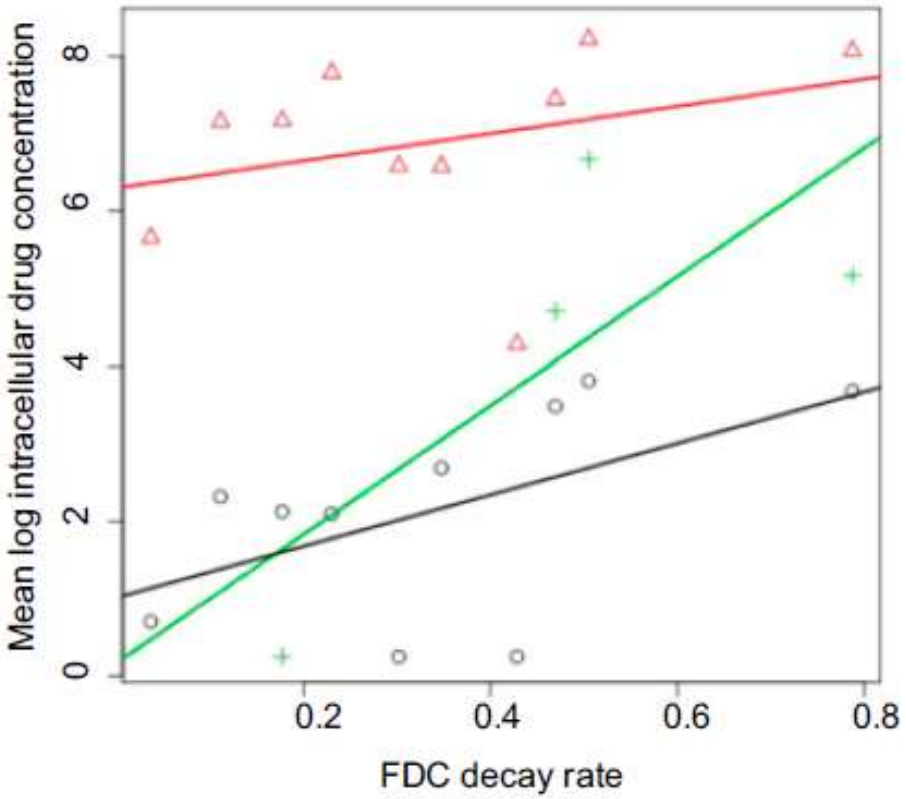
- **Concentration of all drugs remains much lower in the lymph node compared to blood**

Median Percent Difference of LT from PBMC Concentration

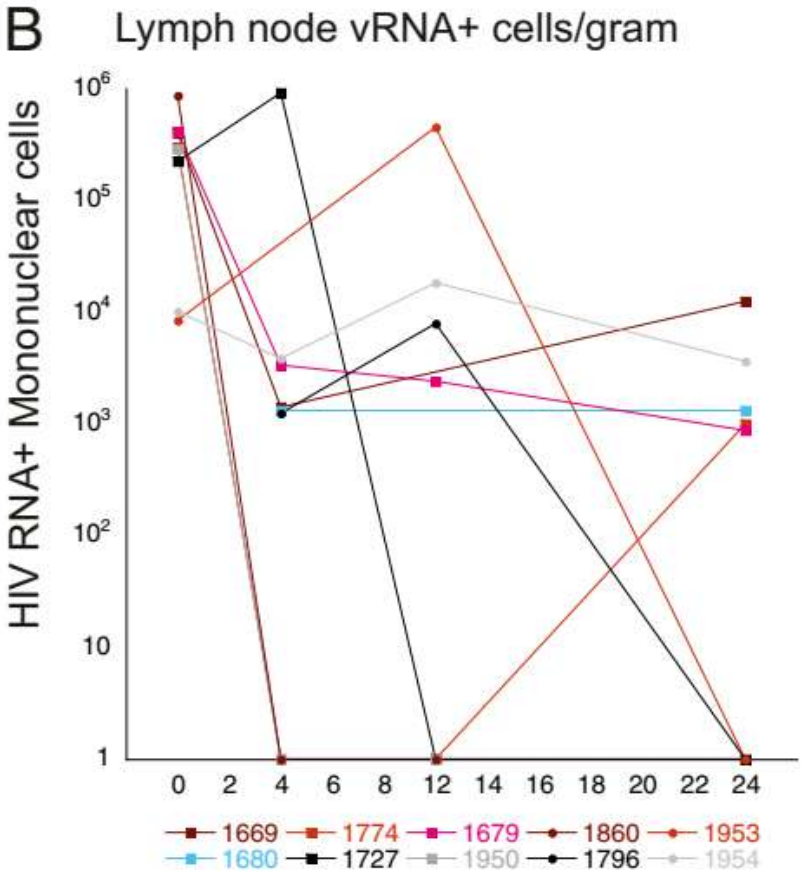


Fletcher, PNAS 2014

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

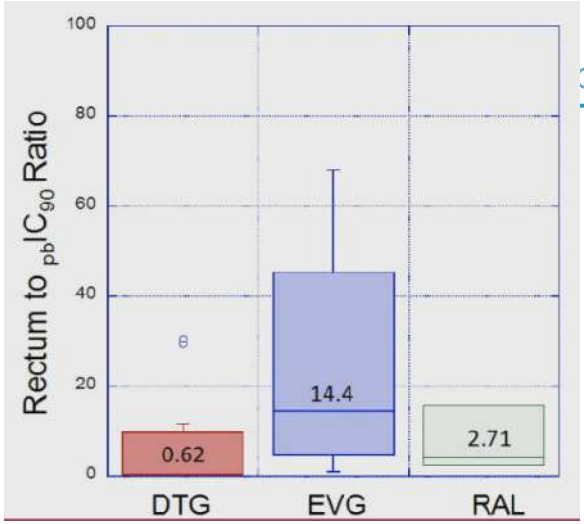


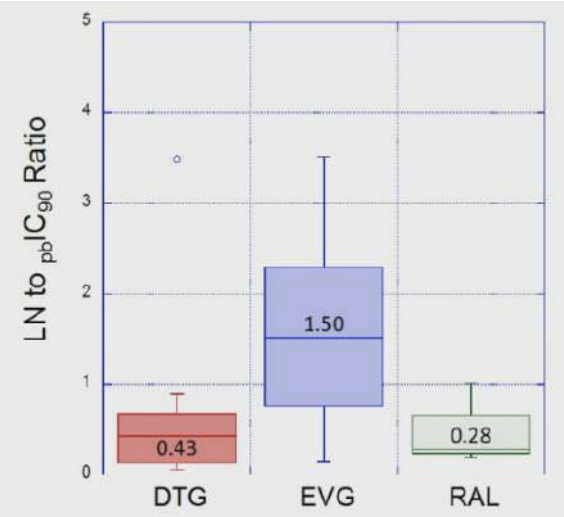
Association between the decay rate of virions from FDC pool and the mean quantity of drug for TFV (black) FTC (red) and EFV (green).

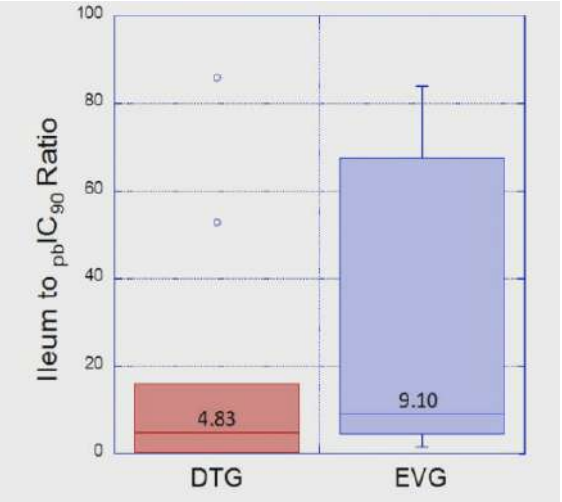


Different rates of decay of individual vRNA+ cells in lymph node under antiretroviral therapy

C.V. Fletcher PNAS 11, 2014







Results: Inhibitory Quotient Values

Matrix	Inhibitory Quotient (intracellular concentration/protein binding corrected IC_{90-95}) Median and Interquartile Range		
	DTG	EVG	RAL
PBMC	6.68 (4.06, 8.16)	9.40 (5.84, 22.84)	6.08 (0.94, 14.14)
LN	0.43 (0.13, 0.67)	1.50 (0.76, 2.29)	0.28 (0.26, 0.48)
Ileum	4.83 (0.38, 16.07)	9.10 (4.51, 65.37)	Not done
Rectum	0.62 (0.33, 9.68)	14.4 (4.65, 169.91)	2.71 (2.62, 5.91)

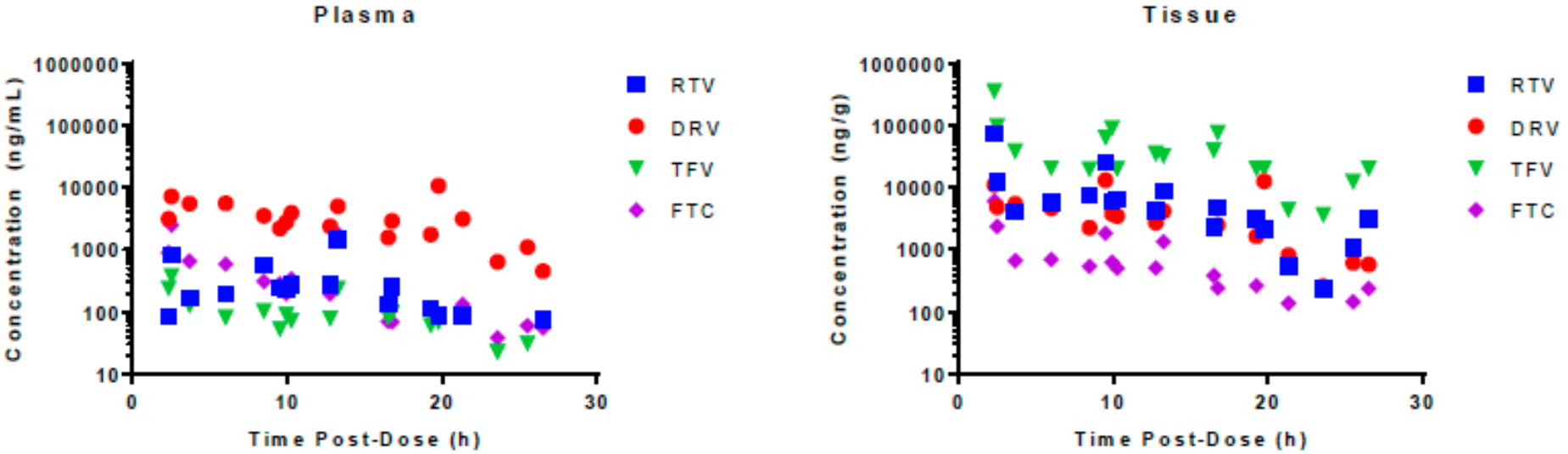
COMPARATIVE LYMPHOID TISSUE PHARMACOKINETICS OF INTEGRASE INHIBITORS.

C. V. Fletcher

CROI 2018

CROI
Conference on Retroviruses and Opportunistic Infections

Exposure of Darunavir, Ritonavir, Emtricitabine, and Tenofovir in Duodenal Tissue: Implications of Gastrointestinal Immune Reconstitution Among HIV-Infected Patients Undergoing ART



Percent of Plasma and Duodenal Tissue Samples with Concentrations Above Inhibitory Targets

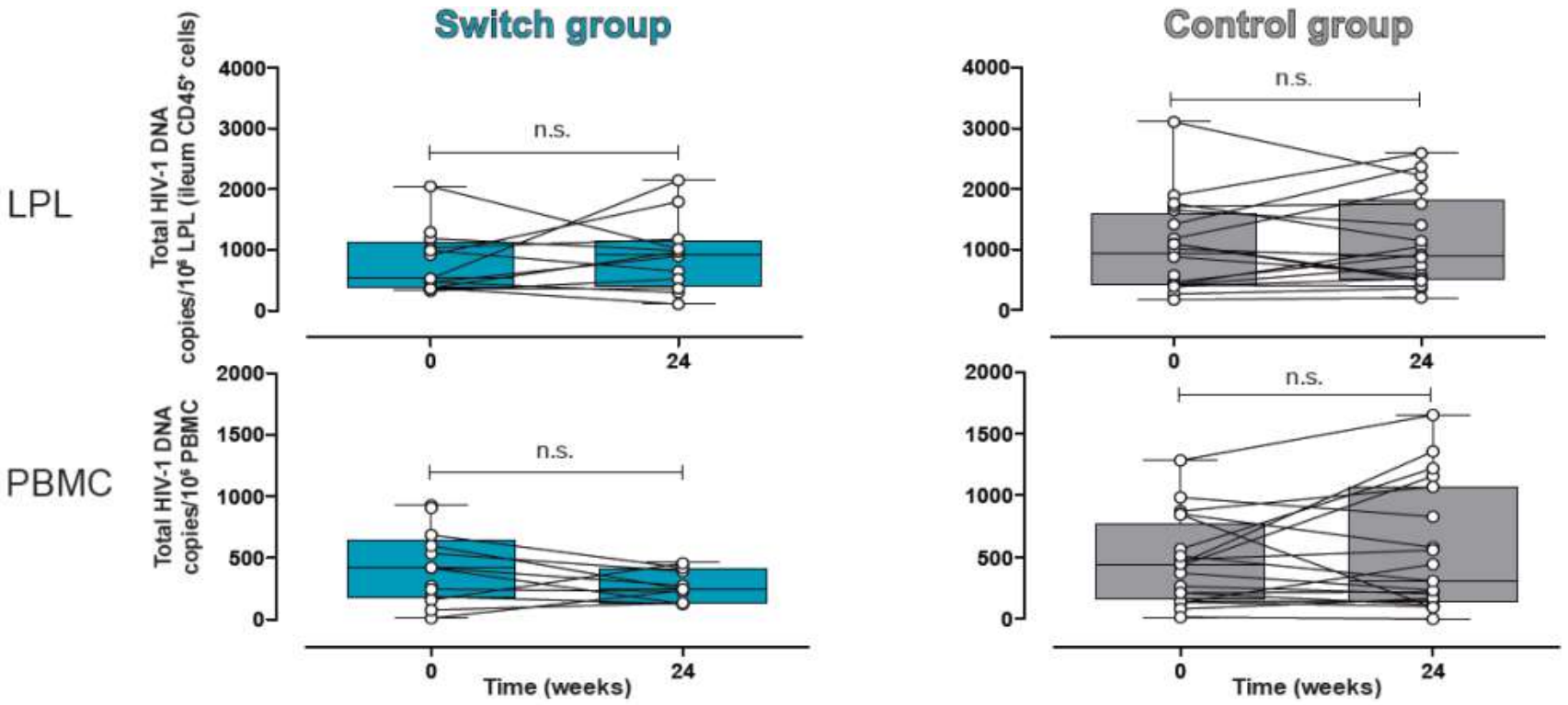
	Ritonavir		Darunavir		Tenofovir		Emtricitabine	
	Plasma	*Tissue*	*Plasma*	*Tissue*	*Plasma*	*Tissue*	*Plasma*	*Tissue*
> IC_{50}	89	100	100	100	0	100	56	78
>10x IC_{50}	56	100	94	94	0	50	11	17
>100x IC_{50}	0	17	22	17	0	6	0	0

Garrett et al. IAS 2017

Effect of Switching to Integrase Inhibitor on the HIV Reservoir in Ileum Biopsies

S. Morón-López et al. CROI 2018

Longitudinal follow up of total HIV reservoir



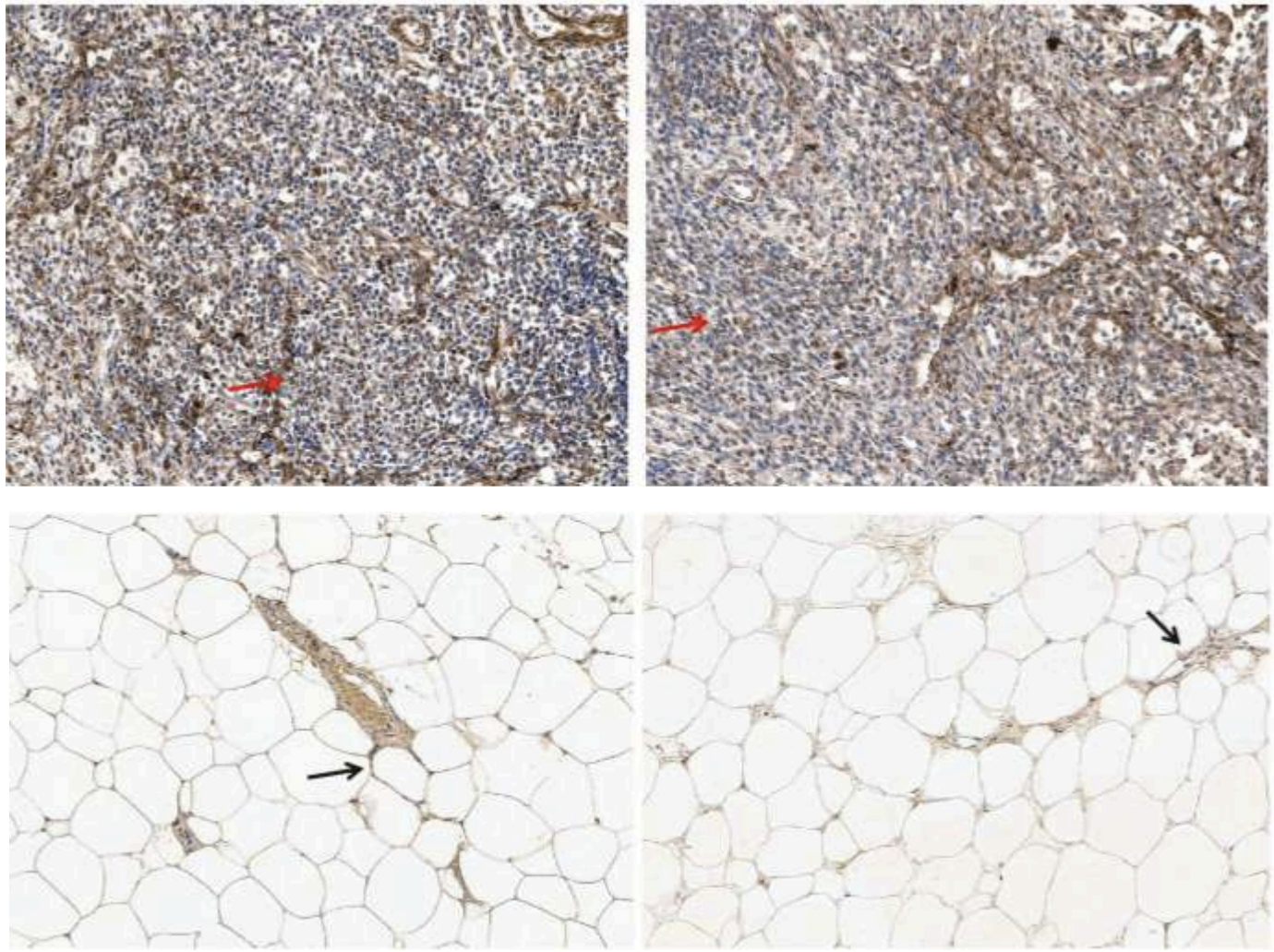
Significant correlation of the HIV reservoir size was observed between tissue and blood samples ($p=0.01$, $Rho=0.43$ at week 0). The reservoir size was consistently higher in tissue CD45+ cells than in PBMC in both groups ($p<0.01$). No significant longitudinal changes in the total HIV reservoir size, either in CD45+ cells of ileum biopsies or in PBMC, in any study group.

Mechanisms and Determinants of ARV Penetration into Lymphatic Tissues

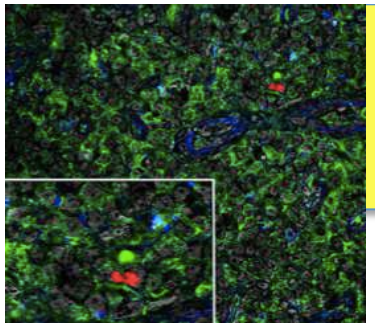
- Portal vein vs. lymph blood flow is 500:1.
  - Most absorbed drugs are preferentially diverted to portal blood.
- Physicochemical characteristics associated with greater lymphatic system penetration: hi molecular weight, larger particle size, log P value > 5, hi long chain TG solubility.
  - All ARVs are low MW compounds and few have log P values > 5.
- Pharmacologic characteristics: distribution and expression of membrane transporters and CYPs in lymphatic endothelial cells and along the GI tract, and ARV substrate specificity.
  - P-gp increases from duodenum to ileum; CYP3A4 decreases from duodenum to colon.
- HIV-associated pathology: lymph node fibrosis.
  - Collagen deposition and resulting fibrosis are correlated with progression to AIDS and less immune reconstitution.

Telmisartan Therapy Does Not Improve Lymph Node or Adipose Tissue Fibrosis More Than Continued Antiretroviral Therapy Alone

Jordan E. Lake,1 for the A5317 AIDS Clinical Trials Group Team 2018;217:1770–81



Collagen I deposition (brown) weaving through the lymph node (LN) (arrow) with disruption of normal architecture.



Reservoir in Lymphatic tissue

Residual viral replication in lymphatic tissues

Chronic inflammation and immunoactivation

Comorbidities and clinical disease

Inhibitory quotient of drugs in lymphatic tissues

ART penetration (simplification)

M. Andreoni April 2018

GEMINI-1 and -2: Objectives

gemini 1
gemini 2

Primary objective[1,2]

To demonstrate the non-inferior antiviral activity of DTG + 3TC QD compared with DTG + TDF/FTC QD over 48 weeks in HIV-1-infected ART-naïve subjects

Secondary objectives[1,2]

- Antiviral activity of DTG + 3TC versus DTG + TDF/FTC at Weeks 24, 96 and 144
- Antiviral activity, immunological effects and disease progression up to study completion of ~7 years
- Viral resistance in subjects meeting CVW criteria
- Safety and tolerability over time
- DTG + 3TC compared with DTG + TDF/FTC: effects on renal and bone biomarkers
- Effects on fasting lipids
- Change in health-related QoL
- Effect of patient characteristics on response to DTG + 3TC or DTG + TDF/FTC over time

CVW, confirmed virologic withdrawal

1. GEMINI-1. Available from: https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed May 2017
2. GEMINI-2. Available from: https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed May 2017