Integrase inhibitors and inflammatory process

Jean-Pierre Routy M.D. FRCPC

McGill Health centre

Vancouver

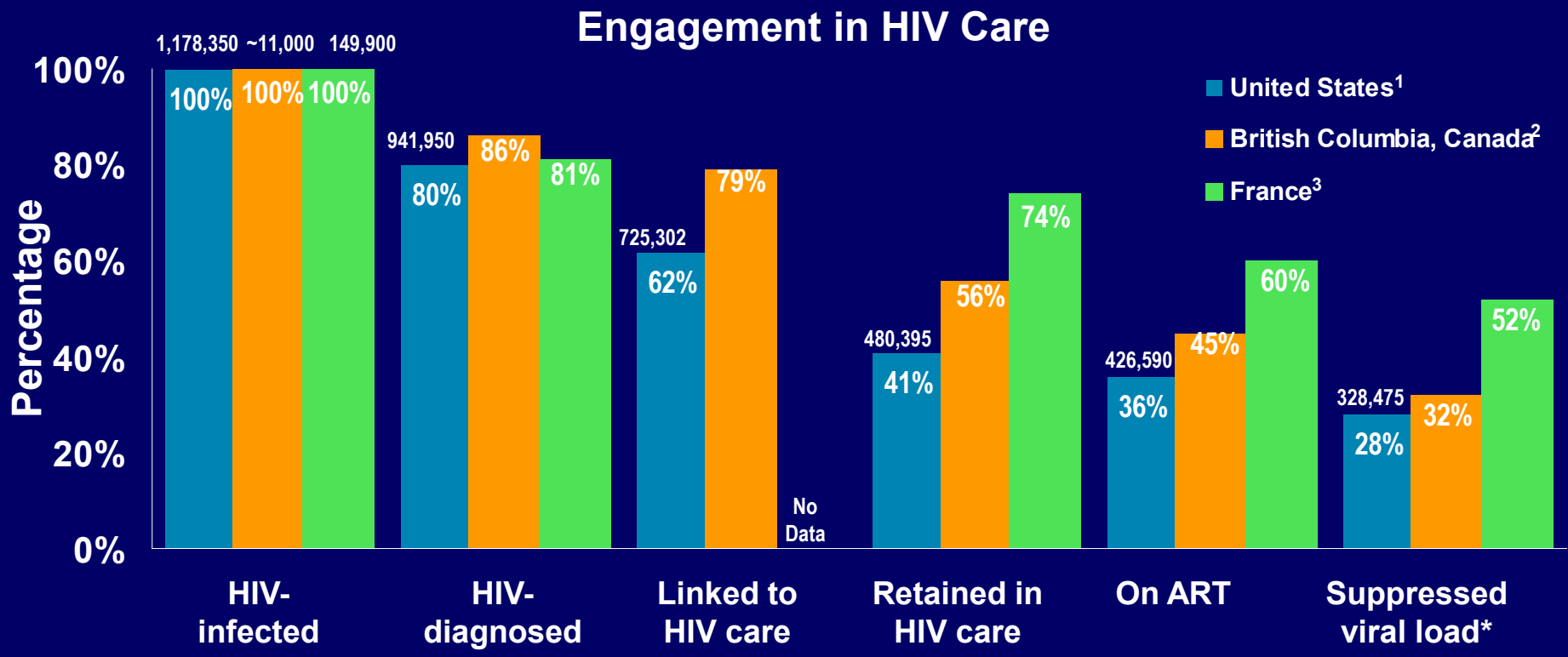
May 25, 2013

HIV, 30 years ago

HIV: Today challenges

- Management:
  - Test, treat, retain in care with best ART
  - Aging
  - Inflammation and non-AIDS events
- Research:
  - Vaccine
  - Eradication
  - Social stigma

Cascade of HIV Care in Various Settings

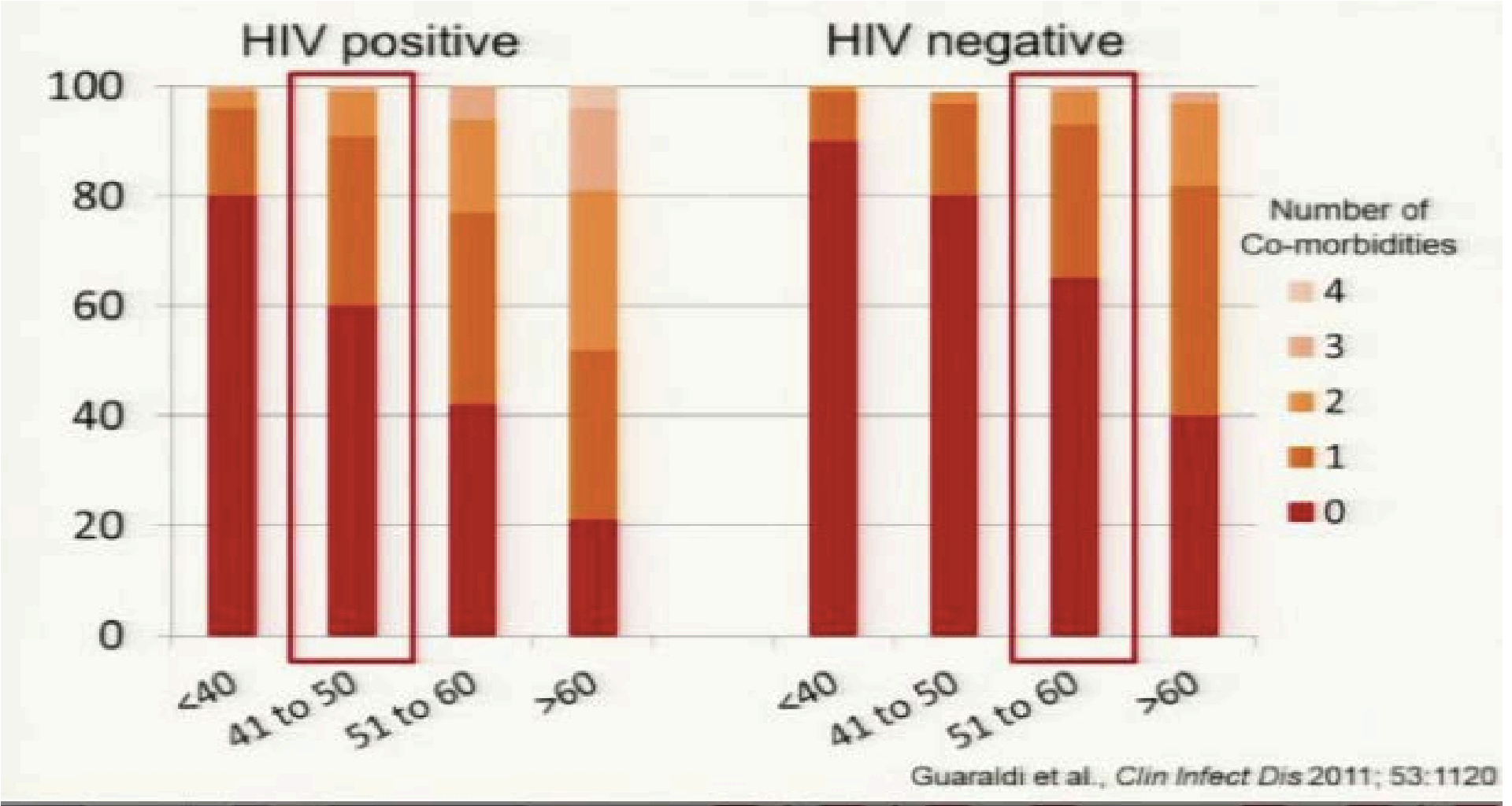


- To achieve a reduction in HIV transmission, HAART programs must ensure the effectiveness and quality of a cascade of services from testing and referral to care to ensuring ongoing adherence to HAART[2]
- Large US cohorts have found that women, IVDU, younger and non-white patients were less likely to achieve virologic suppression, and may require targeted outreach along the cascade of care[4,5,6]

***US ≤200 copies/mL, BC and France < 50 copies/mL**

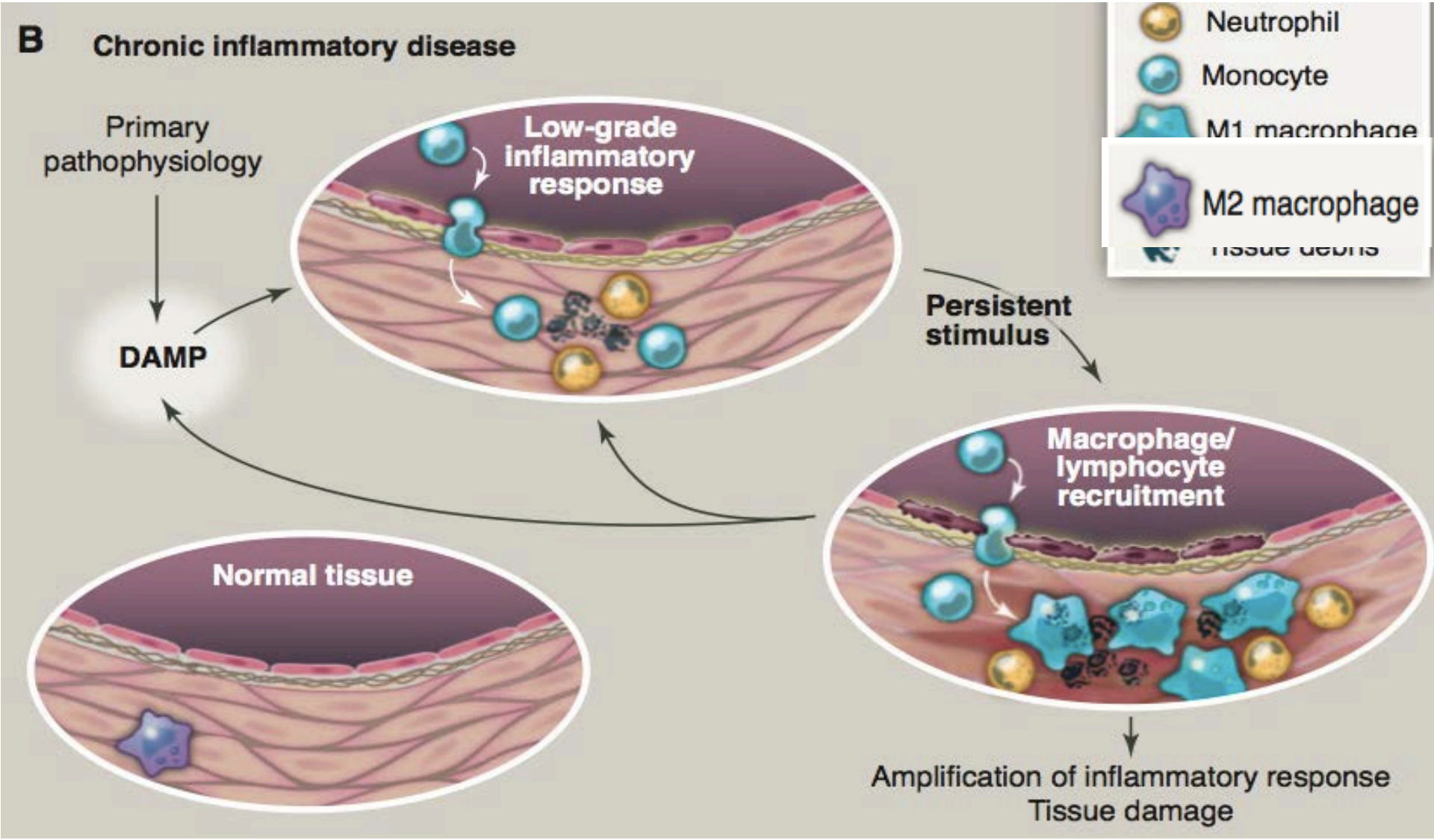
1. Adapted from CDC, MMWR 2011;60:1618-1623
2. Adapted from Nosyk B, et al. CROI 2013; Atlanta, GA. #1029
3. Costagliola D, et al. ibid. #1030
4. Althoff K, et al. ibid. #1026
5. Novak R, et al. ibid. #1032a
6. Horberg M, et al. ibid. #1033

HIV inflammation and comorbidity



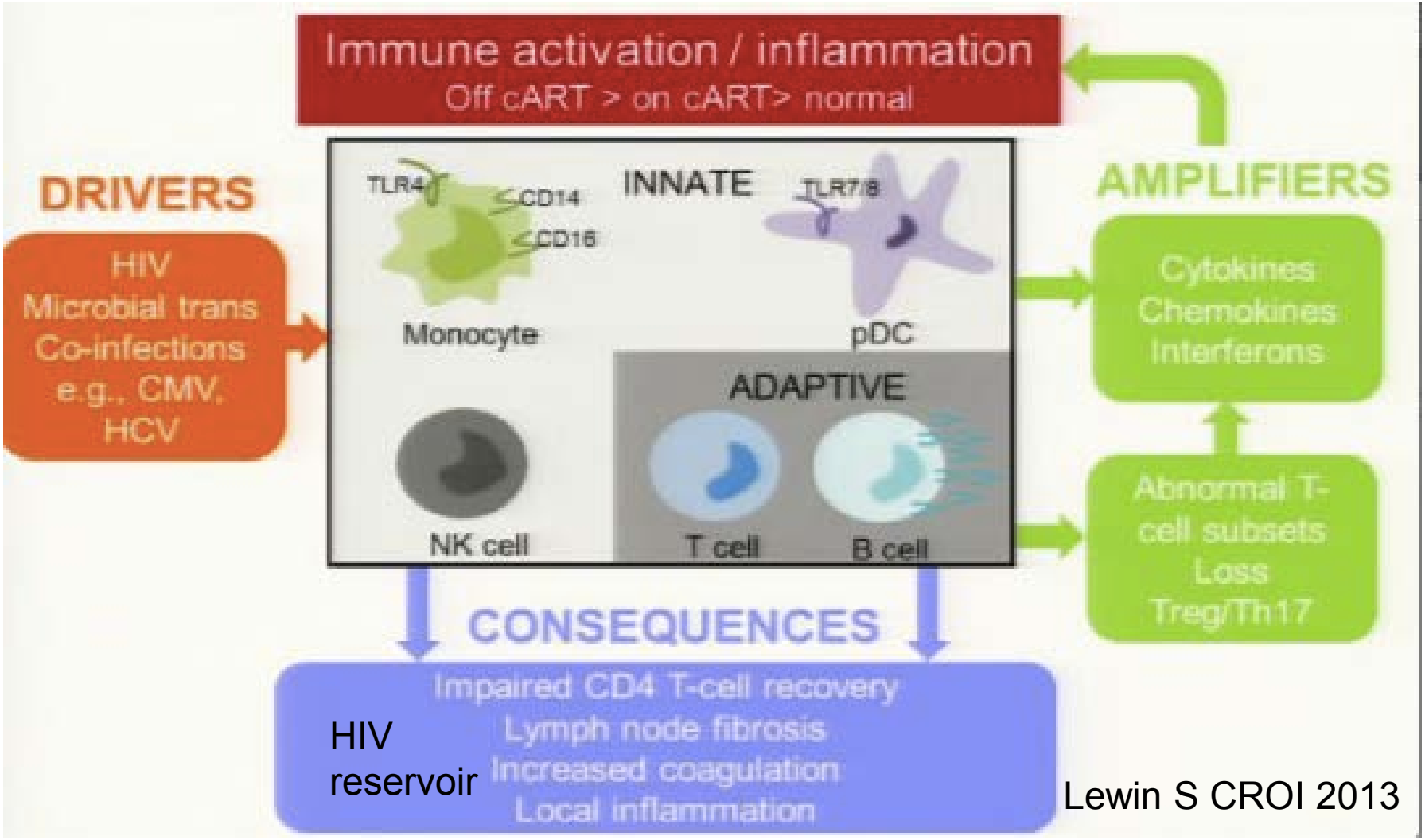
Guaraldi et al., *Clin Infect Dis* 2011; 53:1120

Inflammation and chronic diseases: A commun pathway



Tebas & Glass Science Jan 2013

Inflammation pathway in HIV inflammation



Lewin S CROI 2013


CROI
2013
20th Conference on Retroviruses
and Opportunistic Infections

Inflammation markers and mortality

	SMART/ ESPRIT	FRAM	SOCA/ SCOPE	UARTO	VACS	FIRST (pre ART)
	Case control	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Case control**
T cell activation			✔	✔		
CRP	✔	✔	✔			✔
IL-6	✔		✔			✔
K/T IDO			✔	✔		
Cystatin C		✔				
sCD14	✔		✔		✔	
LPS	**No**					
D-dimer	✔		✔		✔	✔
Fibrinogen		✔				

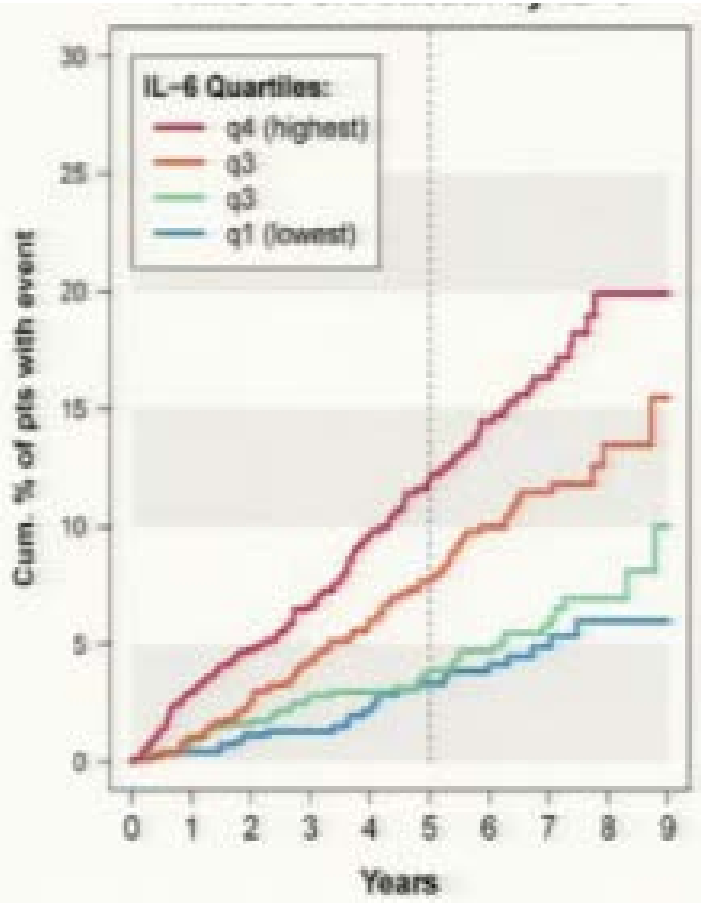
Lewin S CROI 2013

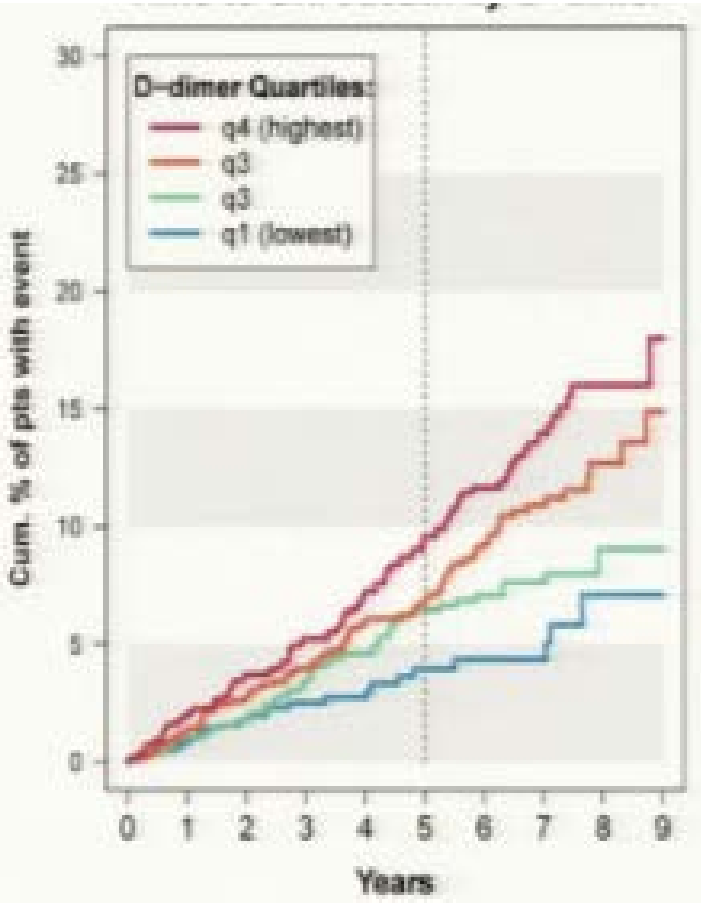
Inflammation markers and non-AIDS events

	CV disease	Cancer	Bone disease	HAND	Liver disease	
	1,2	3,4	5	6,7	HCV[8,9]	HBV[9]
T cell activation	✔		✔	✔		
CRP	✔	✔	✔			
IL-6	✔	✔	✔		✔	✔
sCD168	✔			✔		
Cystatin C				✔		
sCD14	✔	✔		✔	✔	✔
LPS	✔	✔		✔	✔	
D-dimer	✔					✔

Hsue et al *Journal of American Heart Asso* 2012; 2 Burdo et al., *J Infect Dis* 2011; 204:154; [3] Marks et al., *AIDS* 2013, 27(3):469-74; [4]Borges et al., AIDS 2013 (in press) [5] Morse CG et al., *AIDS* 2013;27; [6] Ancuta P, *et al*, *PLoS One* 2008;3:e2516; [7] Lyons et al., *J Acquir Immune Defic Syndr*. 2011 Aug 15;57(5):371-9(4):591-5; [8] Balagopal A, *et al*. *Gastroenterology* 2008;135:226–233 [9] Sereti et al., *J Infect Dis* 2013 (epub)

Time to non-AIDS events and death association with IL-6 and D-dimers



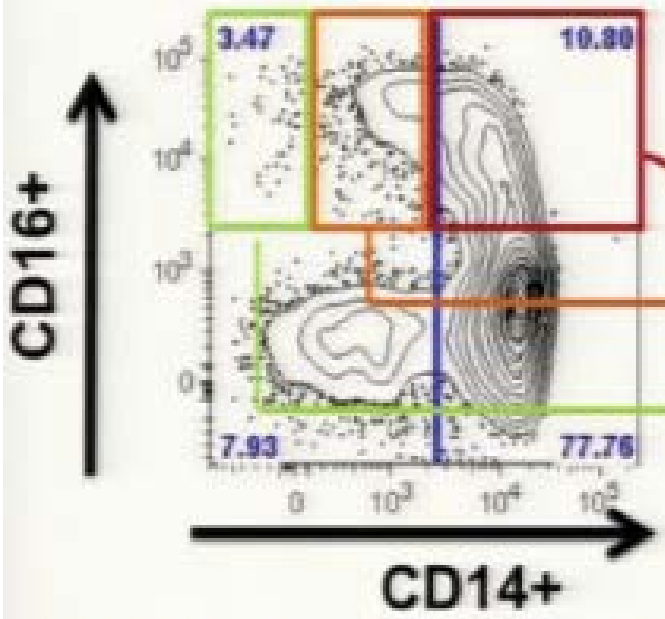


N= 3766, control arms of the SMART, ESPRIT and SILCAAT trials, all on ART
Mean CD4=500cells/ul; mean follow up for 5 years

CROI 2013

CD16+ monocytes independently predict progression of coronary artery ca^{++}

n=436; SUN cohort; longitudinal study of coronary artery Ca++ (CAC) over 2 years



CD16+ monocytes are "inflammatory"

CD14 hi

CD14 var

CD14 neg

Predict risk of CAC progression

Monocyte Phenotype (%)	OR (95% CI) for CAC Progression*	p-value
CD14+/CD16+	1.65 (1.08, 2.52)	0.02
CD14^{var}/CD16+	1.69 (1.12, 2.54)	0.01
CD14-/CD16+	1.36 (0.98, 1.88)	0.06

*no association with T-cell activation markers

Baker et al., 20th CROI 2013 abstract #66LB

REVIEW ARTICLE

MECHANISMS OF DISEASE

Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy

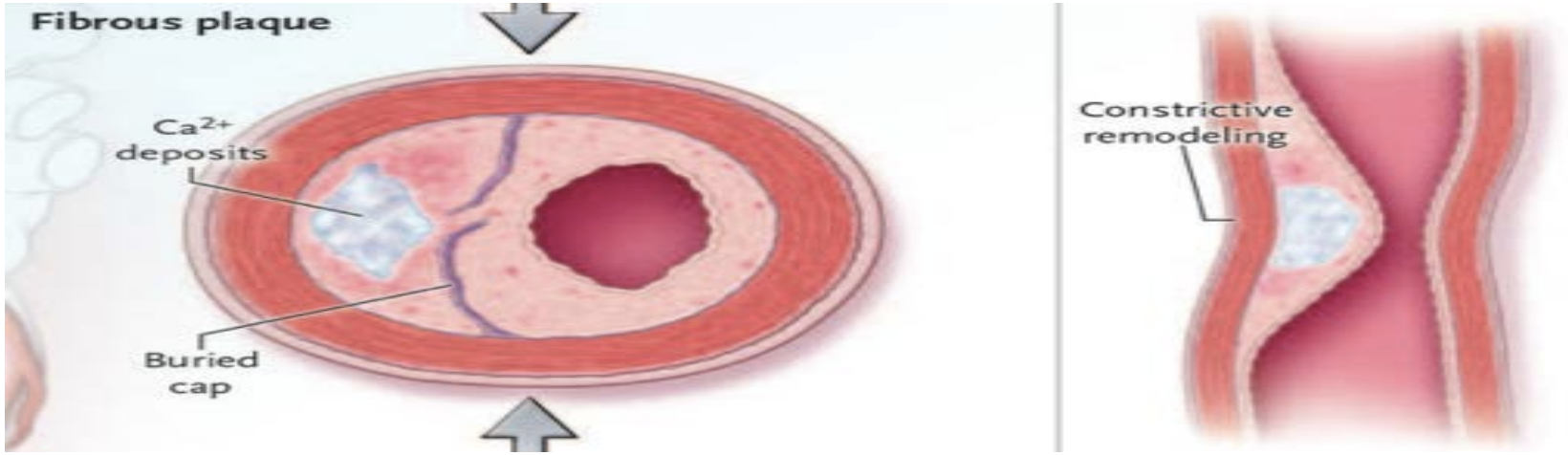
Peter Libby, M.D.

INFLAMMATION, COLLAGEN METABOLISM, AND PLAQUE RUPTURE AND THROMBOSIS

N ENGL J MED 368;21 NEJM.ORG MAY 23, 2013

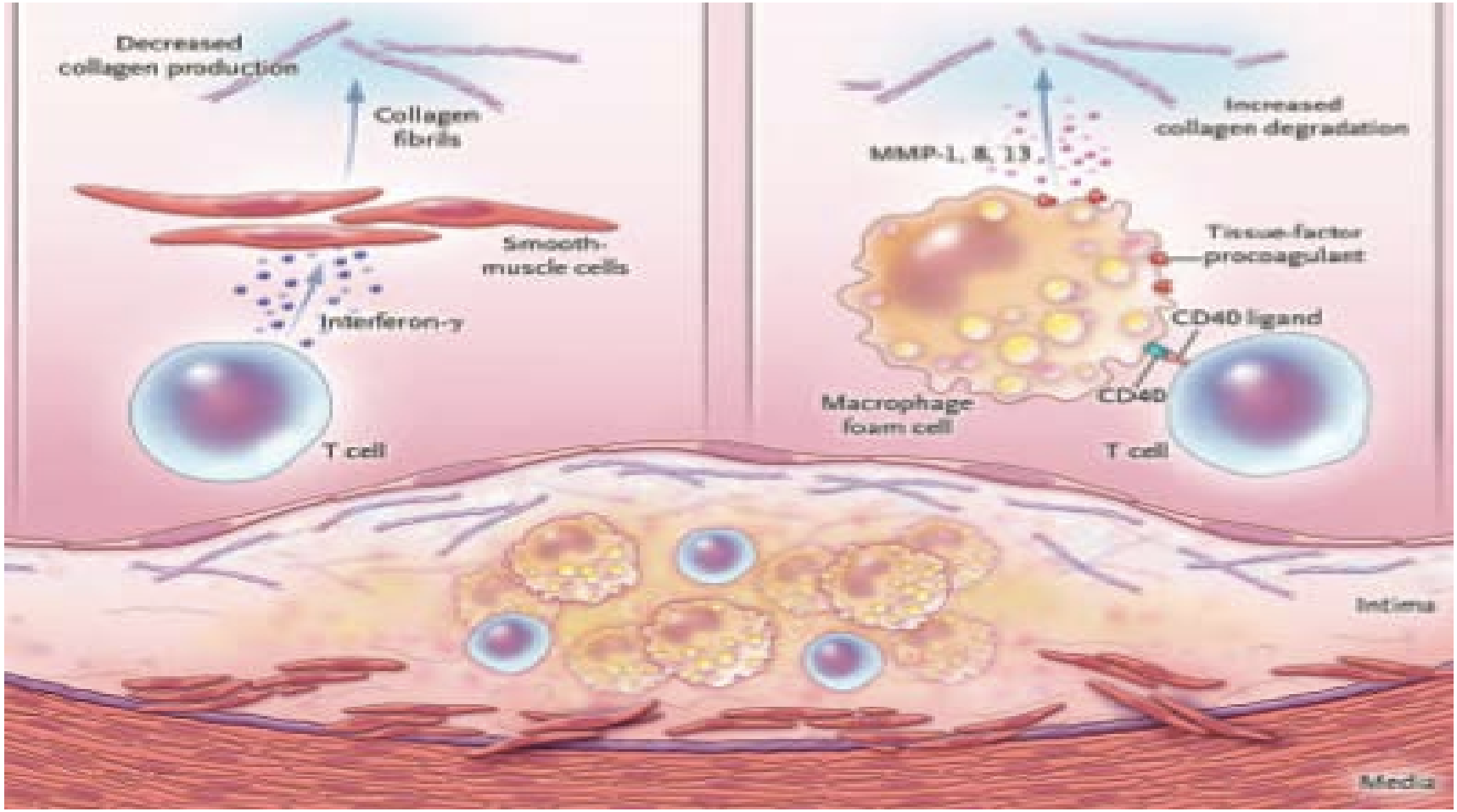
Macrophages and atherosclerosis

- Macrophages and atherosclerosis lesions and thrombi
- Overproduction of 3 matrix-metalloproteinase (MMP) interstitial collagenases:
  - MMP-1, MMP-8, and MMP-13



N ENGL J MED 368;21 NEJM.ORG MAY 23, 2013

Inflammation predisposing coronary arteries to rupture and thrombosis



N ENGL J MED 368;21 NEJM.ORG MAY 23, 2013

Contribution of classes of ART on HIV-related inflammation ?

- NRTIs:
  - Mitochondrial toxicity
- NNRTI:
  - Mild lipid effect (sustiva)
- PIs:
  - Lipid changes, ritonavir
- Integrase inhibitors:
  - Not well defied

Integrase inhibitors

Table 1 Major characteristics of the 3 INSTIs

Characteristic	RAL	EVG/cobi	DTG
Dosing	400 mg bid	150/150 mg qd	50 mg qd in INSTI-naive and 50 mg bid in INSTI-experienced patients
STR	No	Yes (TDF/FTC/EVG/cobi)	Together with abacavir(ABC) and 3TC
To be taken with food	No	Yes	No
In vitro activity*	33 nM (IC_{95})	45 ng/mL (IC_{95})	0.064 µg/mL (0.15 µM) (IC_{90})
Protein binding	83%	98 %	99.3%
Terminal half-life	9 h	12.9 h/3.5 h	15 h
Drug-drug interactions	with inducers of UGT1A1 (rifampin)	Presence of a strong CYP3A inhibitor such as cobicistat creates the potentialfor an increase in systemic exposure of CYP3A substrates	with inducers of UGT1A1 (rifampin)
Interaction with proton pump inhibitors and antacids	No	No	No

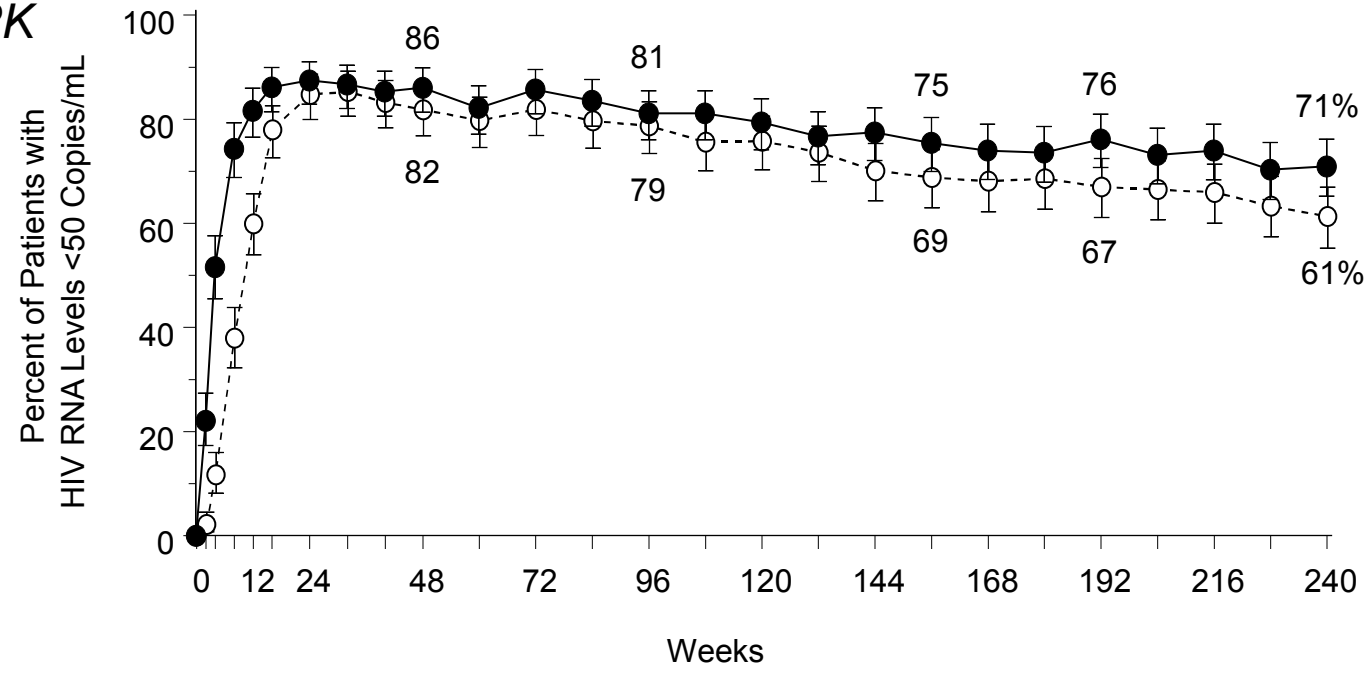
Mutations			
	E92Q	T66I/A/K	H51Y
	Y143C/H/R	E92Q/G	R263K
	Q148 H/K/R	T97A	

Mesplede et al Retrovirol 2013

Proportion (%) of Patients Achieving HIV RNA <50 (95% CI) Over Time

Final 5-Year Double-Blind Results From STARTMRK

Non-Completer = Failure Approach

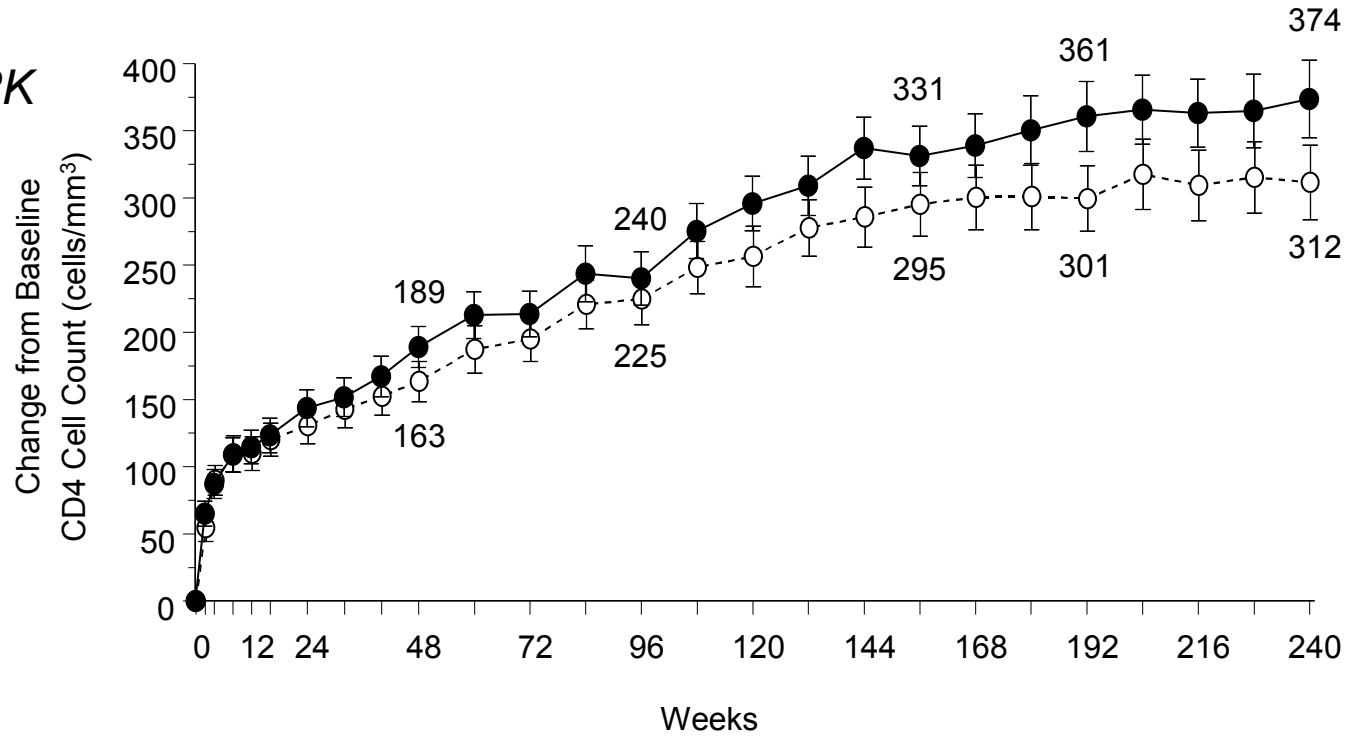


Number of Contributing Patients

● Raltegravir 400 mg bid.	281	278	279	280	281	281	277	280	281	281	277	279
○ Efavirenz 600 mg qHS.	282	282	282	281	282	282	281	281	282	282	282	279

Change From Baseline in CD4 Over Time

Final 5-Year Double-Blind Results From STARTMRK



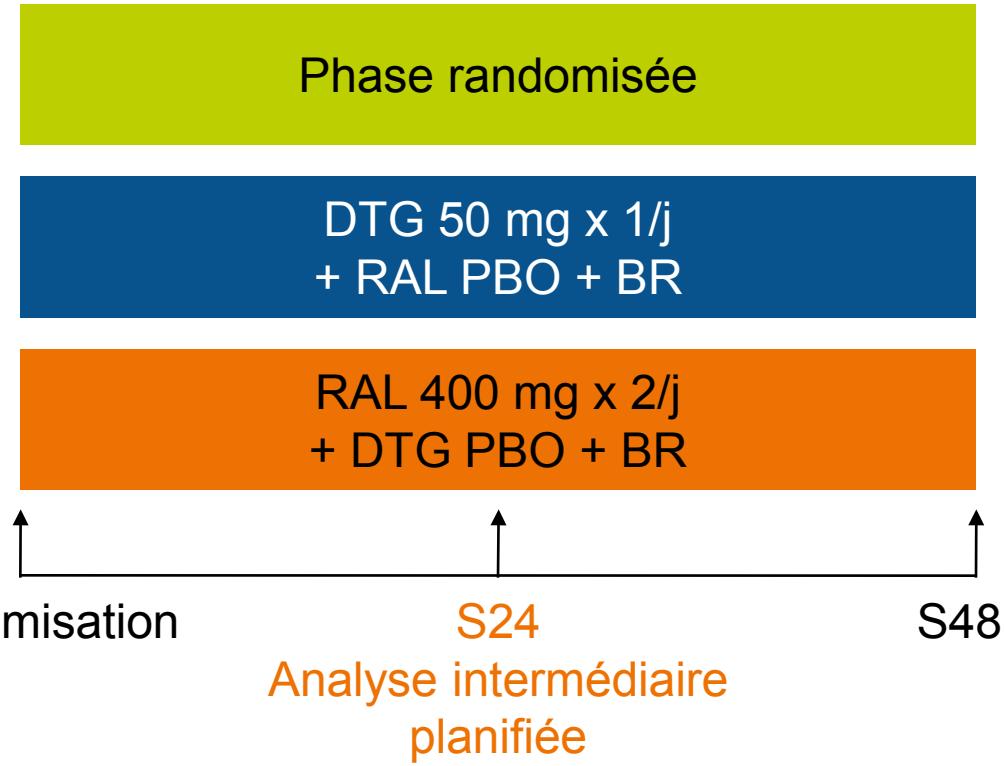
Number of Contributing Patients

● Raltegravir 400 mg bid.	281	272	266	258	255	250	240	235	231	235	227	222
○ Efavirenz 600 mg qHS.	281	268	266	251	252	243	234	228	224	220	218	212

SAILING : DTG versus RAL chez les patients prétraités naïfs d'INI – résultats à S24

- **Étude randomisée de phase III en double aveugle**

Patients prétraités,
naïfs d'INI
CV > 400 copies/ml*
Randomisation 1:1
stratification selon la CV initiale (≤ ou > 50 000), l'administration de DRV/r et de molécules pleinement actives



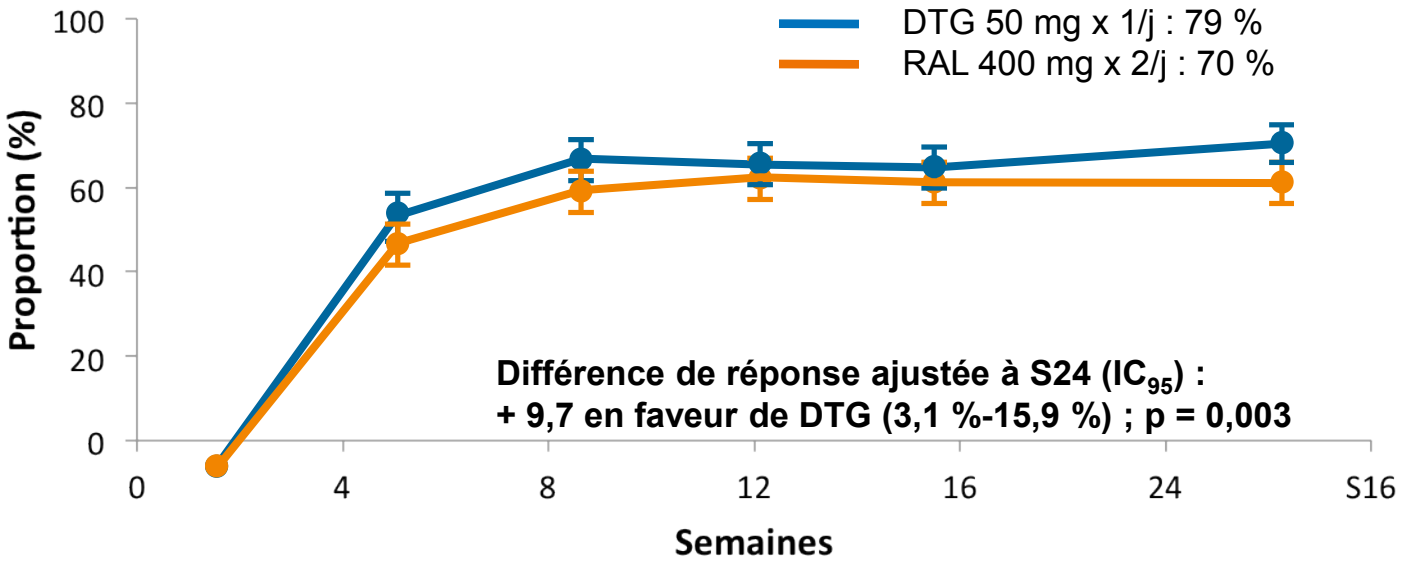
* À l'inclusion et un 2e test consécutif > 400 copies/ml dans les 4 mois précédant l'inclusion (si CV à l'inclusion > 1 000 copies/ml, pas d'indication à un 2e test).
PBO : placebo ; BR : traitement associé.

CROI 2013 – D'après Pozniak A. et al., abstract 179LB, actualisé

SALING

- **Résultats (1) : pourcentage de patients avec CV < 50 copies/ml à S24 (*Snapshot*, ITTm)**

DTG 50 mg x 1/j est statistiquement supérieur à RAL 400 mg x 2/j à S24

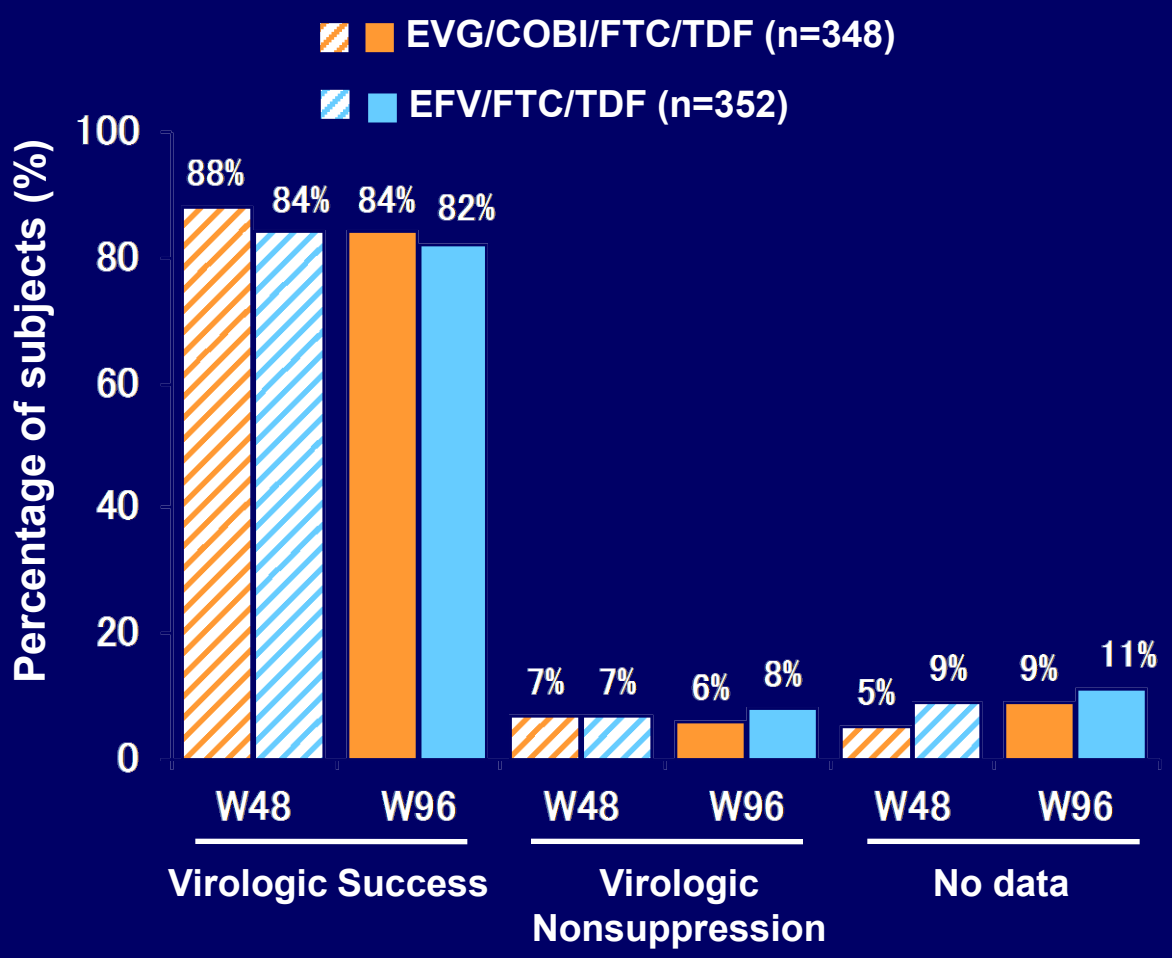


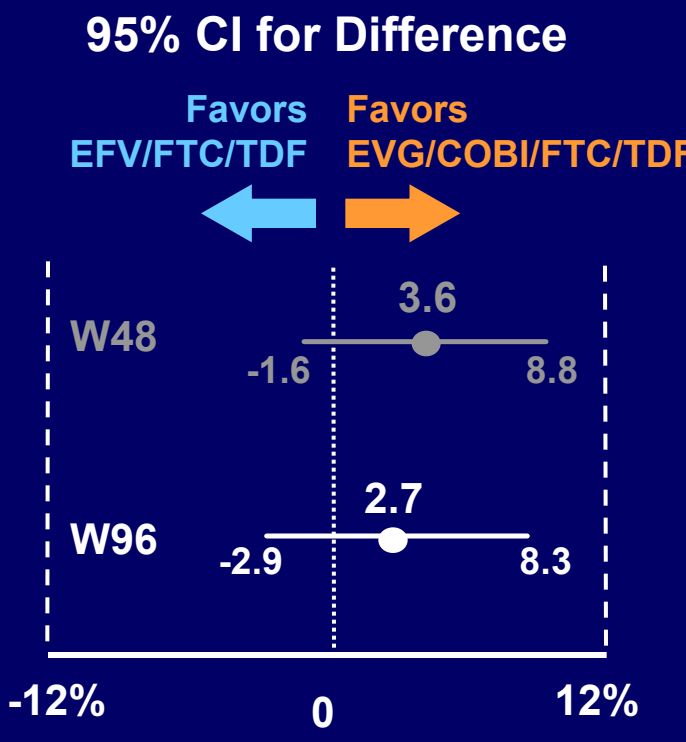
➜ **Efficacité immunologique comparable : + 99 (DTG) vs + 93 (RAL) cellules/mm³**

CROI 2013 – D'après Pozniak A. et al., abstract 179LB,

Study 102

Efficacy Endpoint: HIV-1 RNA <50 c/mL





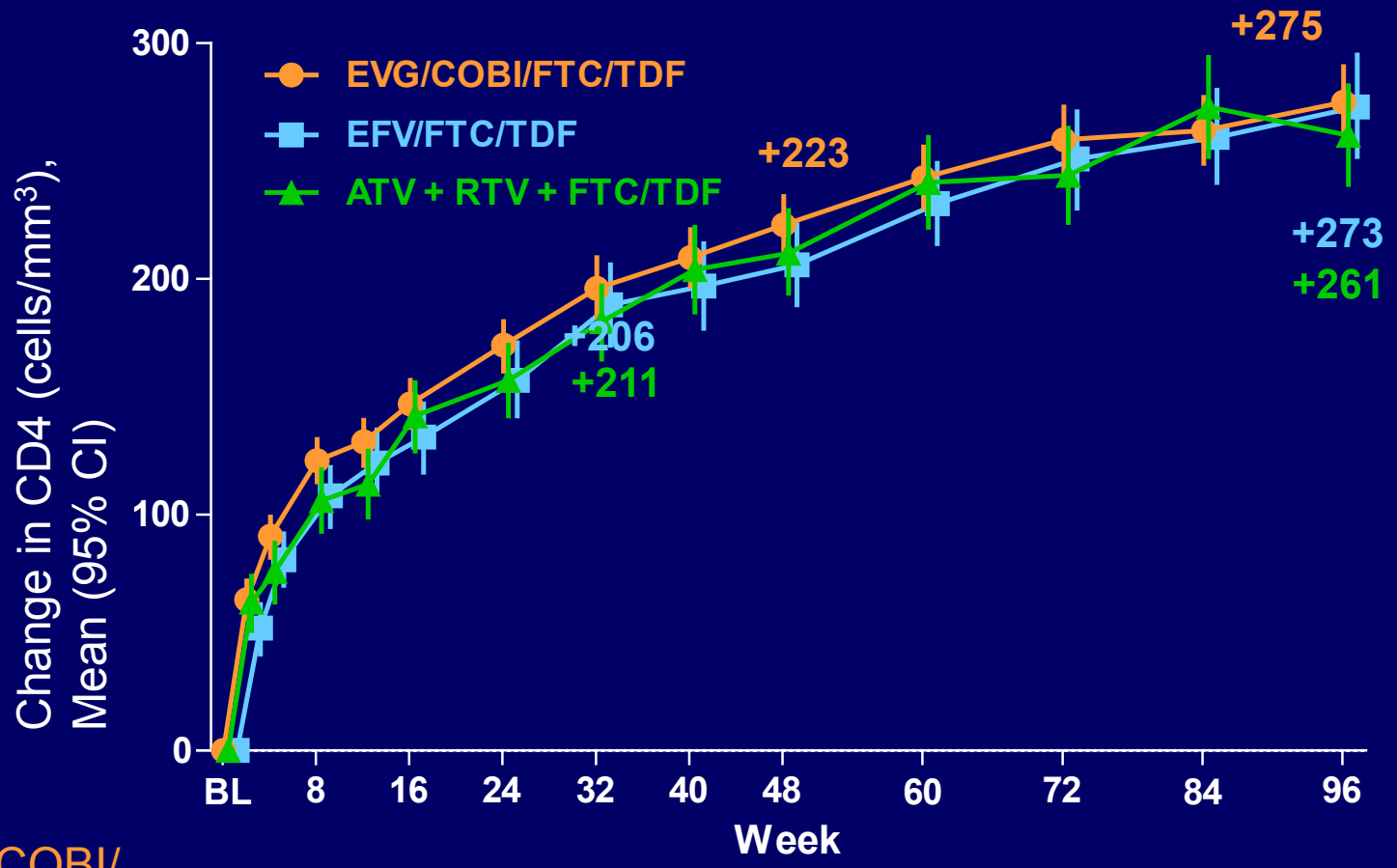
Virologic success (HIV-1 RNA <50 c/mL) as defined by FDA Snapshot algorithm

1. Zolopa A, et al. CROI 2013; Atlanta, GA. #553

2. Zolopa A, et al. JAIDS. E-published, Feb 2013

Integrated Study 102 and 103 - Week 96

Change from Baseline in CD4 Cells

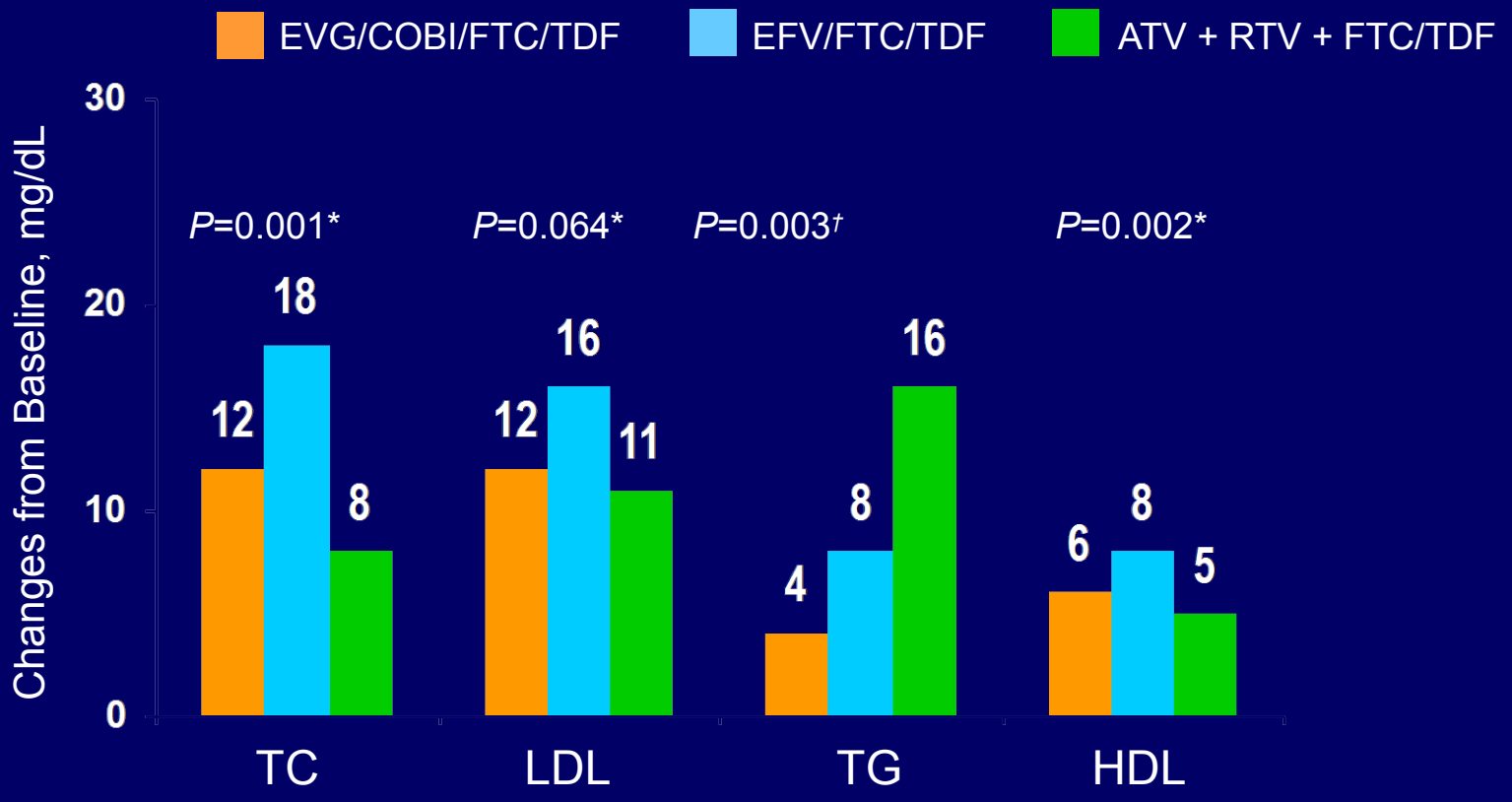


EVG/COBI/FTC/TDF (n=)	701	686	673	660	654	653	659	653	630
ATV + RTV + FTC/TDF (n=)	627	623							
EFV/FTC/TDF (n=)	352	339	325	322	317	314	315	312	311

Zolopa A, et al. CROI 2013; Atlanta, GA. #553

Integrated Study 102 and 103 - Week 96

Change from Baseline in Fasting Lipids



No difference in change in TC:HDL ratio at Week 48 or 96

* *P*-value for EVG/COBI/FTC/TDF vs. EFV/FTC/TDF
† *P*-value for EVG/COBI/FTC/TDF vs. ATV + RTV + FTC/TDF

Zolopa A, et al. CROI 2013; Atlanta, GA. #553

Integrase inhibitor and inflammation

- All associated with:
  - Faster V.L. decay than any PI or NNRTI
  - Higher CD4 recovery on long-term
  - No significant impact on lipid

- Raltegravir and its impact on:
  - Inflammation
  - HIV reservoir

Poster
O-190

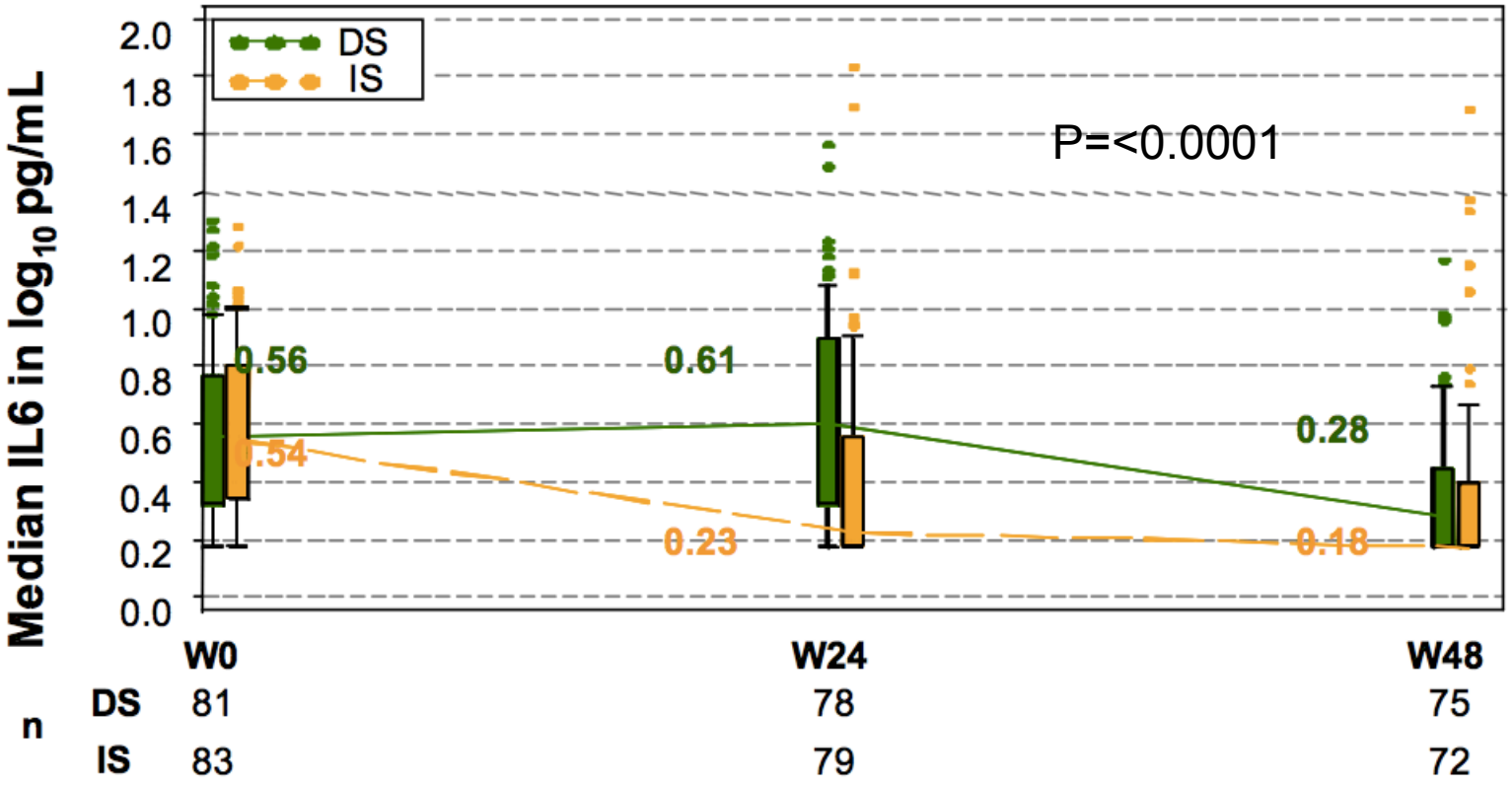
Decrease in Inflammatory and Coagulation Biomarkers in HIV-Infected Patients After Switching from Enfuvirtide to Raltegravir in the Randomized ANRS 138 EASIER Trial

Erika Silva [1], Isabelle Charreau [2], Bernard Gourmel[1], Samia Mourah [1], Issa Kalidi [1], Brigitte Guillon [2], Nathalie De Castro [1], François Caron [3], Josephine Braun [2], Jean-Michel Molina[1] and the ANRS Easier study group.

[1]AP-HP-Hôpital Saint-Louis, Université Paris 7, PARIS, [2]INSERM SC10, VILLEJUIF, [3]Hôpital Universitaire Charles Nicolle ,ROUEN, all in France.

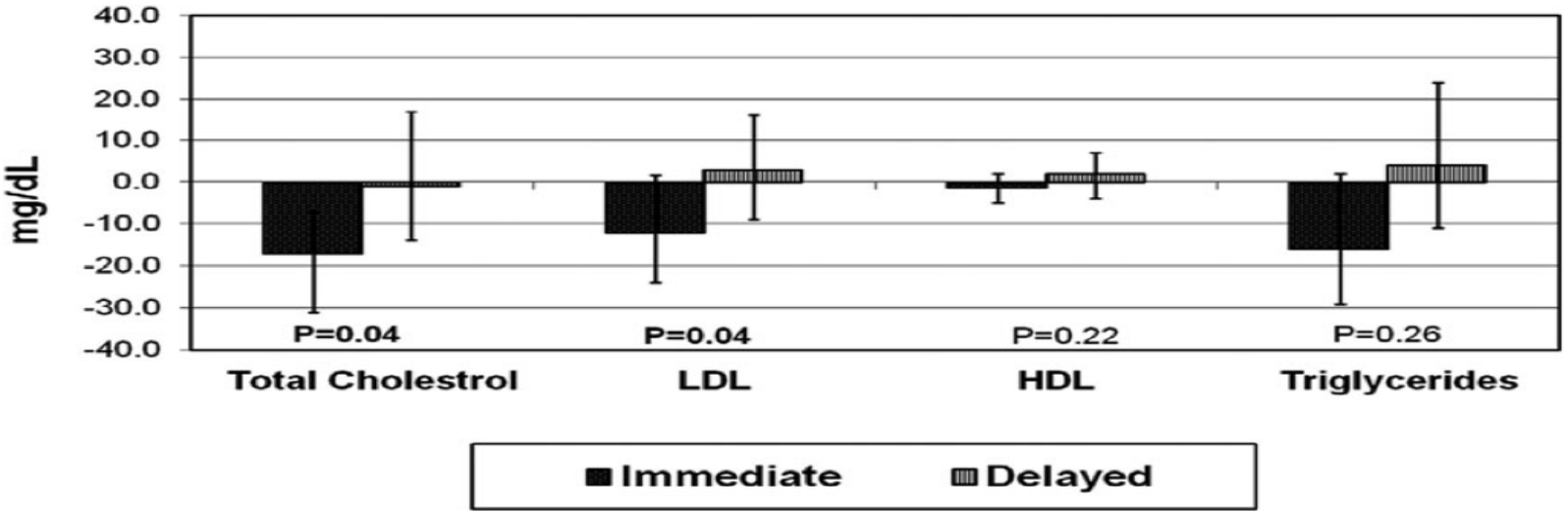
Figure 1: IL6 levels in log_{10} (pg/mL)

DS: Delay Switch
IS: immediate Switch



A Randomized Trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor in HIV-Infected Women with Lipohypertrophy

Jordan E. Lake, M.D., M.Sc.,[1] Grace A. McComsey, M.D.,[2] Todd M. Hulgan, M.D., M.P.H.,[3]
Christine A. Wanke, M.D.,[4] Alexandra Mangili, M.D., M.P.H.,[4] Sharon L. Walmsley, M.D., M.Sc.,[5]
M. Sean Boger, M.D., PharmD,[6] Ralph R. Turner, Ph.D., M.P.H.,[7]
Heather E. McCreath, Ph.D.,[1] and Judith S. Currier, M.D., M.Sc.[1]



well with percent visceral AT change. No RAL-related adverse events occurred. Compared to continued PI or NNRTI, switch to RAL was associated with statistically significant 24-week improvements in total and LDL cholesterol but not AT volumes. Additional insights into AT and metabolic changes in women on RAL will be provided by 48-week follow-up of the immediate-switch arm.

AIDS PATIENT CARE and STDs
Volume 26, Number 9, 2012

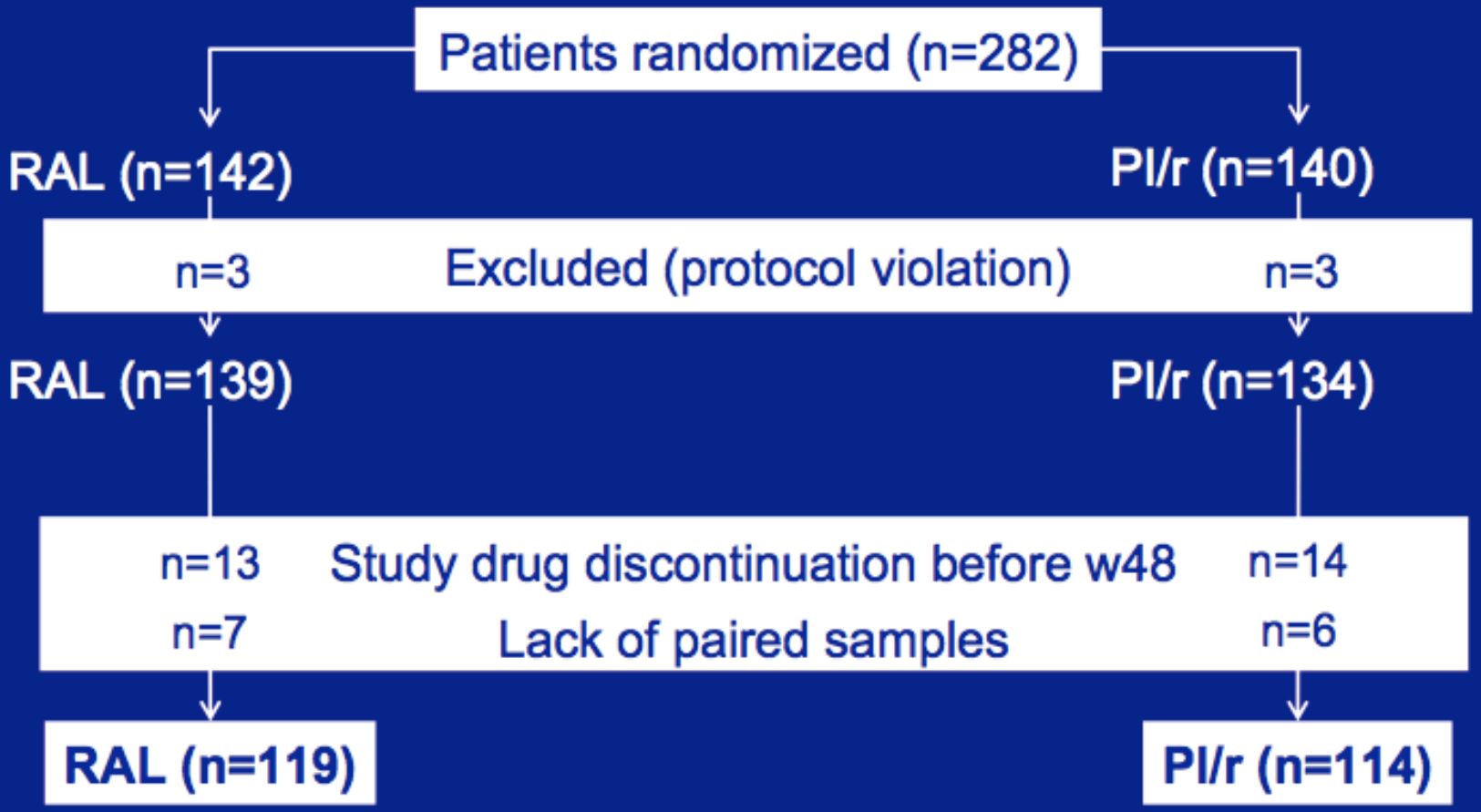
Changes in Cardiovascular Biomarkers in Subjects Switching from Ritonavir-Boosted Protease Inhibitors to Raltegravir: The SPIRAL Study.

E Martinez[1], P Monteiro[1], JM Llibre[2], F Gutierrez[3], D Podzamczer[4], A Antela[5], J Berenguer[6], I Perez[1], J Pich[1], JM Gatell[1], and the SPIRAL Study Group.

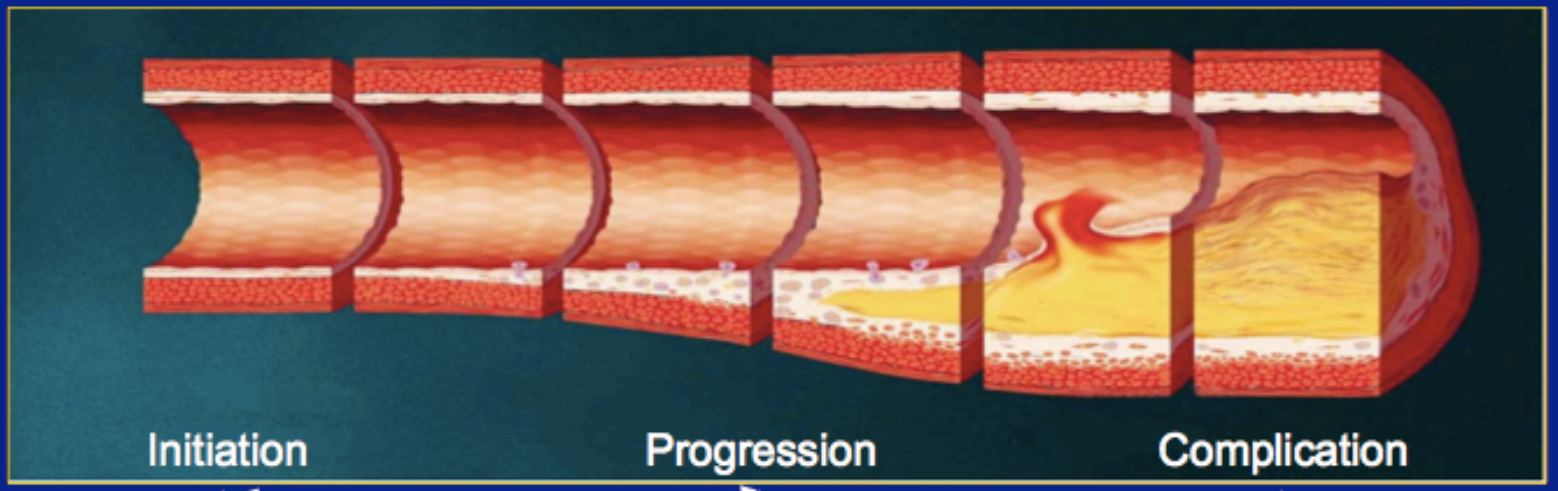
1 Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona;2 Germans Trias i Pujol University Hospital and Lluita contra la SIDA Foundation, Badalona; 3 Hospital General Universitario de Elche, Elche; 4 Hospital Universitari de Bellvitge, L`Hospitalet de Llobregat; 5 Complexo Hospitalario Universitario de Santiago, Santiago de Compostela; and 6 Hospital General Universitario Gregorio Marañón, Madrid, all in Spain.

SPIRAL Cardiovascular Biomarkers Sub-study: Participants

- Stable HIV-infected adults (≥ 18 years)
- PI/r plus ≥ 2 non-PI antitretrovirals
- HIV-RNA < 50c/mL for ≥ 6 months
- No prior RAL use



Biomarkers and lipids measured at baseline and 48 weeks



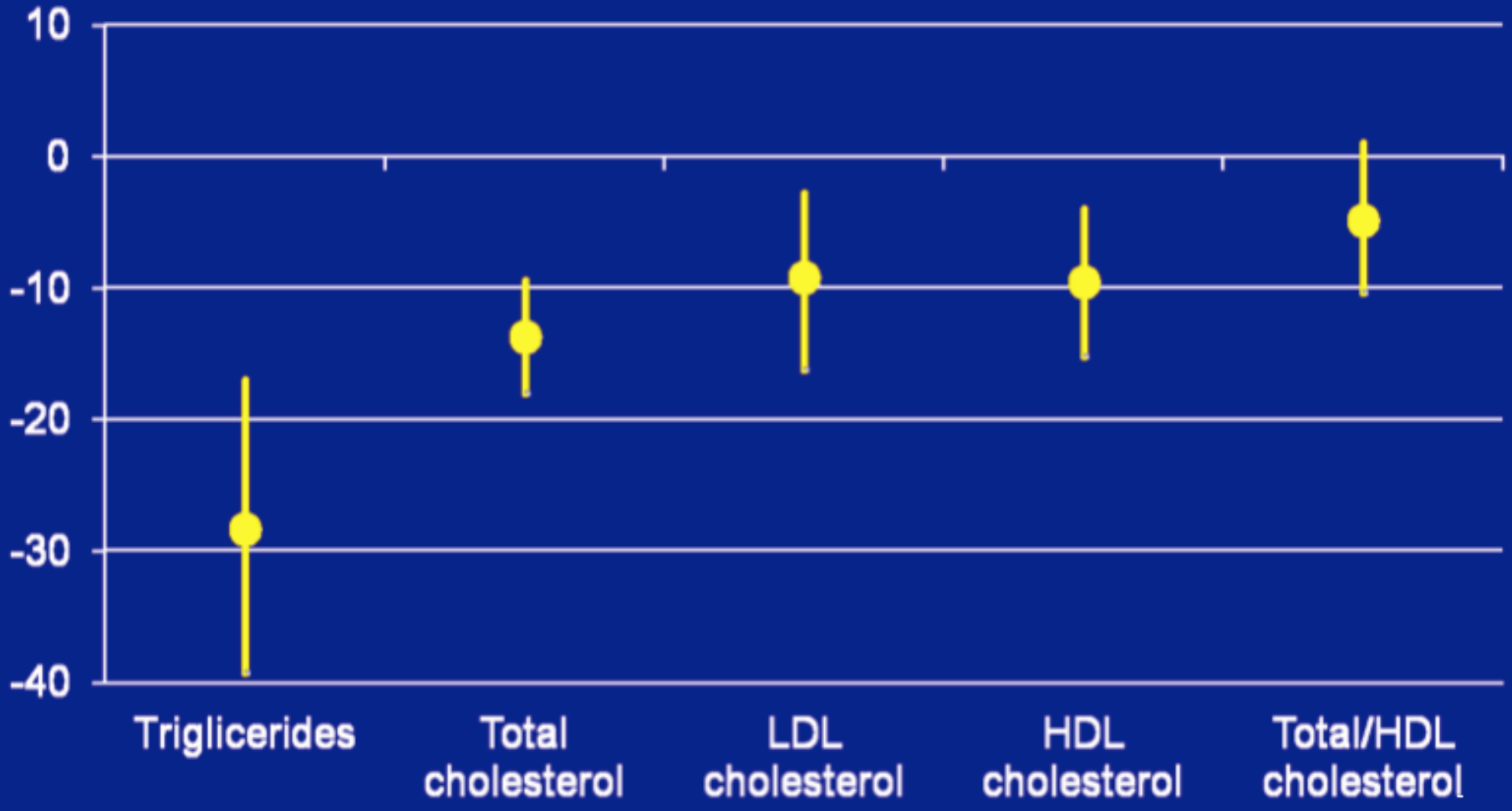
Inflammation	Endothelial dysfunction Insulin resistance	Hypercoagulability
hsCRP, MCP-1 OPG, IL-6 TNF-alpha, IL-10	**ICAM-1, VCAM-1 E-Selectin, P-Selectin Insulin, Adiponectin**	**D-dimer**

Lipids (fasting)	**Triglycerides, Total cholesterol, LDL cholesterol, HDL cholesterol**

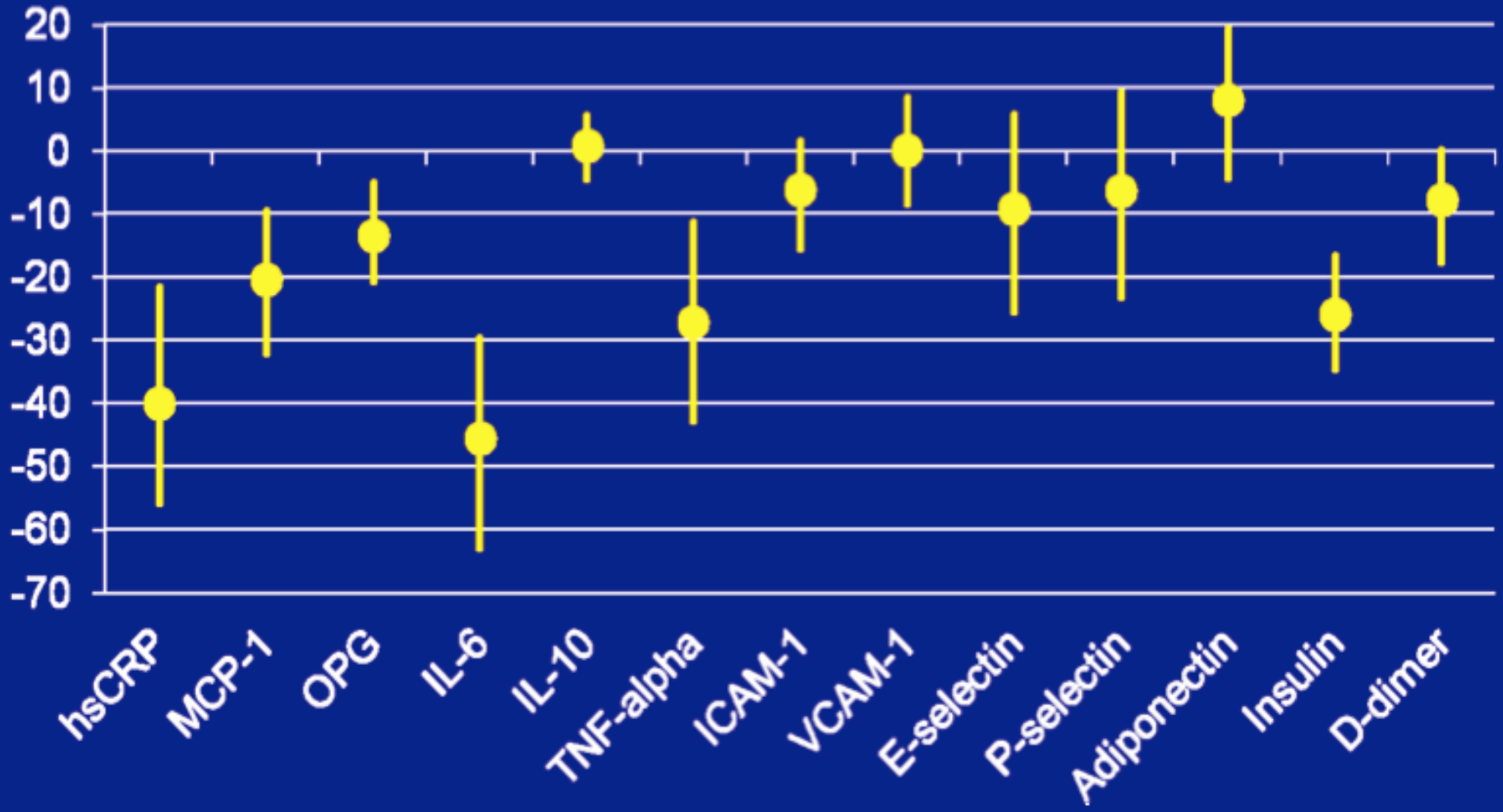
Characteristics of participants

	RAL (n=119)	PI/r (n=114)
Age, years (IQR)	43 (40-49)	44 (40-50)
Men (n, %)	94 (79)	83 (73)
NRTI backbone at entry (n, %)		
3TC/FTC plus TDF	69 (58)	64 (56)
3TC/FTC plus ABC	24 (20)	23 (20)
3TC/FTC plus AZT	9 (8)	10 (9)
Other	17 (14)	17 (15)
PI/r at entry (n, %)		
LPV/r	52 (44)	54 (47)
ATV/r	45 (38)	40 (35)
Other	22 (18)	20 (18)
Patients on 1st ART (n, %)	15 (13)	14 (12)
ART exposure, years (median, range)	10 (5-12)	10 (6-12)
PI exposure, months (median, range)	31 (19-45)	30 (17-50)
Previous suboptimal ART or virological failure (n, %)	68 (55)	55 (48)
Patients with AIDS (n, %)	43 (36)	42 (37)

Lipids: Median difference of percent change RAL minus PI/r (95% CI)



Biomarkers: Median difference of percent change RAL minus PI/r (95% CI)

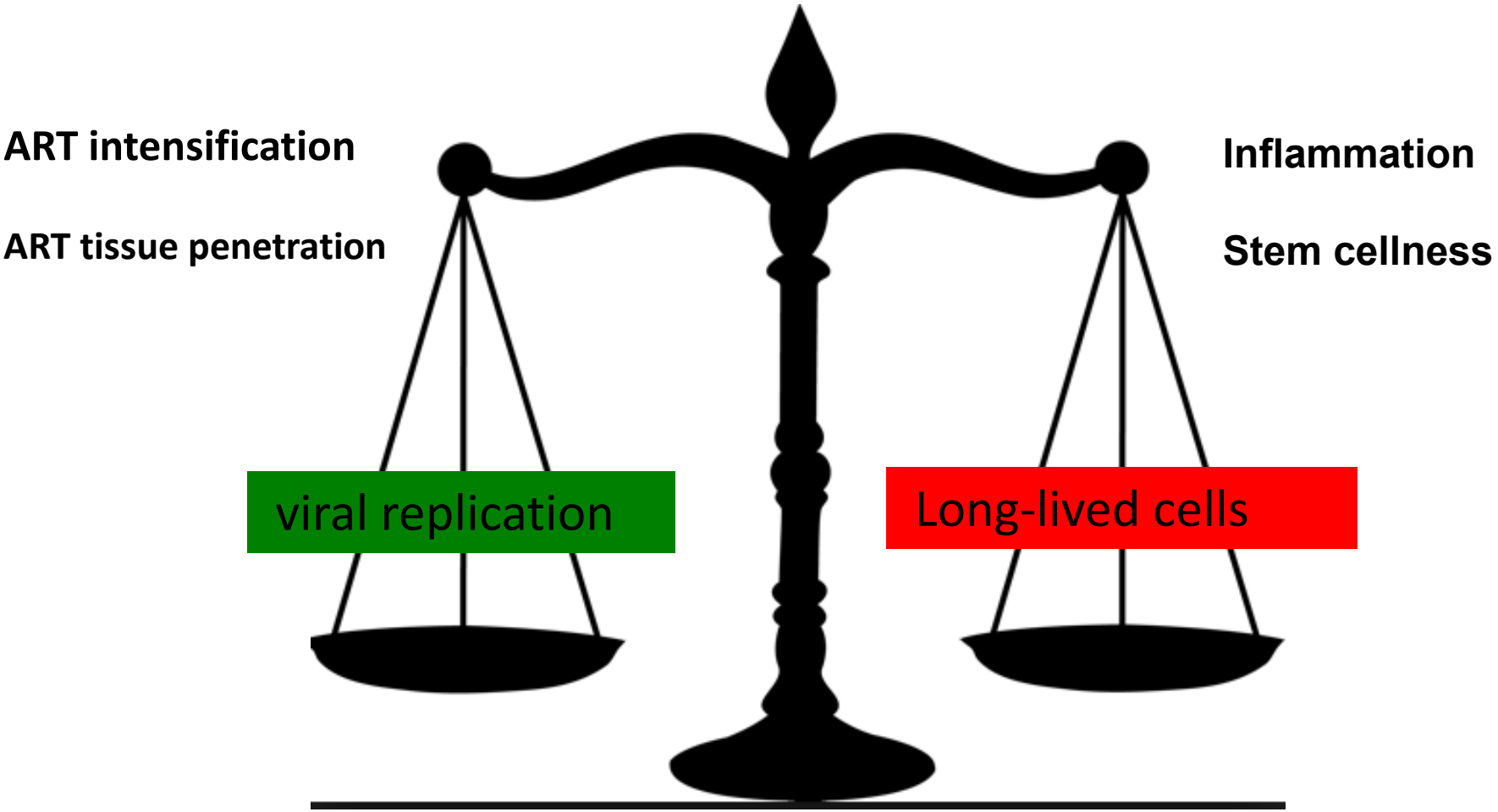


Correlations between Δ biomarkers and Δ lipids

	ΔTriglycerides	ΔTotal cholesterol	ΔLDL cholesterol	ΔHDL cholesterol
ΔhsCRP	-	-	Spearman's rho 0.2415 (P=0.0016)	-
ΔMCP-1	-	Spearman's rho 0.1608 (P=0.0320)	-	Spearman's rho 0.1807 (P=0.0202)
ΔOPG	-	-	-	-
ΔIL-6	-	-	-	-
ΔIL-10	-	-	-	-
ΔTNF-alpha	-	-	-	-
ΔICAM-1	-	-	-	-
ΔVCAM-1	-	-	-	-
ΔE-selectin	-	-	-	-
ΔP-selectin	-	-	-	-
ΔAdiponectin	-	-	-	-
ΔInsulin	Spearman's rho 0.2842 (P=0.0001)	Spearman's rho 0.2125 (P=0.0040)	-	-
ΔD-dimer	-	-	-	-

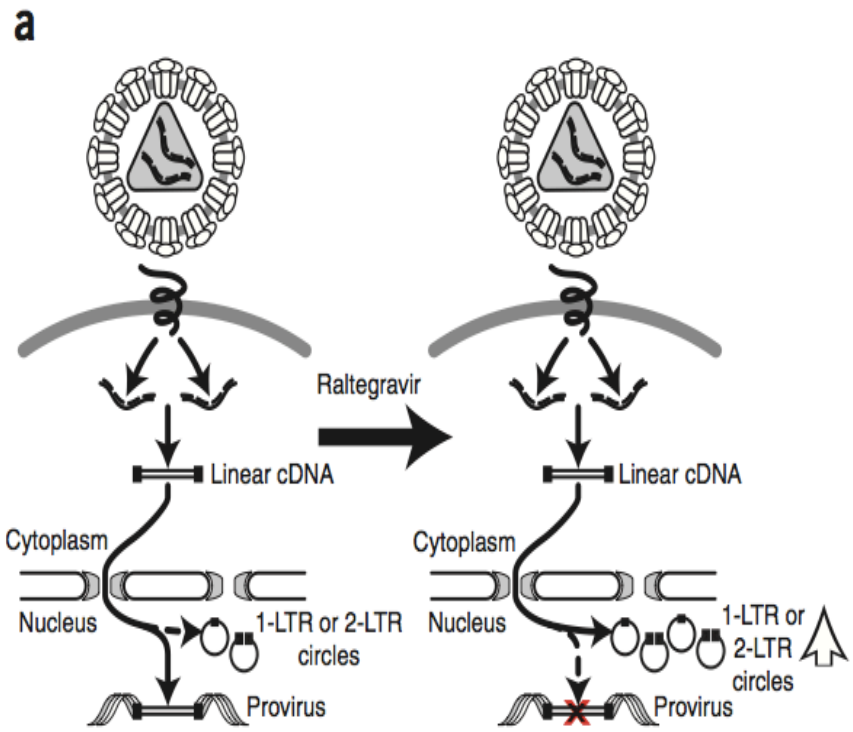
Only correlations showing a P value <0.005 are shown

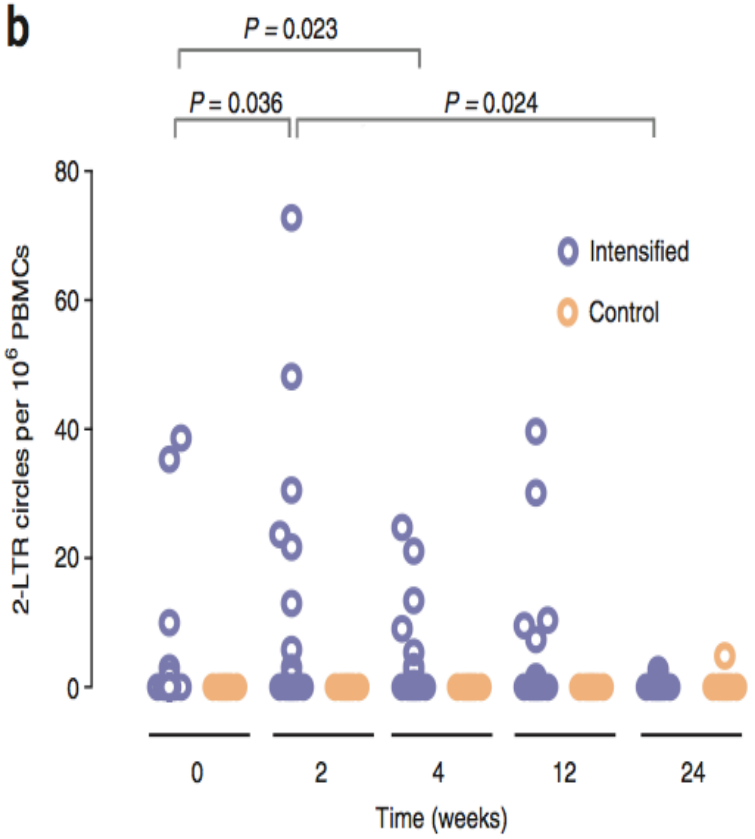
HIV reservoirs and Raltegravir



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

Maria J Buzón[1,9], Marta Massanella[1,9], Josep M Llibre[2], Anna Esteve[3], Viktor Dahl[4], Maria C Puertas[1], Josep M Gatell[5], Pere Domingo[6], Roger Paredes[1,2], Mark Sharkey[7], Sarah Palmer[4], Mario Stevenson[7], Bonaventura Clotet[1,2], Julià Blanco[1] & Javier Martinez-Picado[1,8]



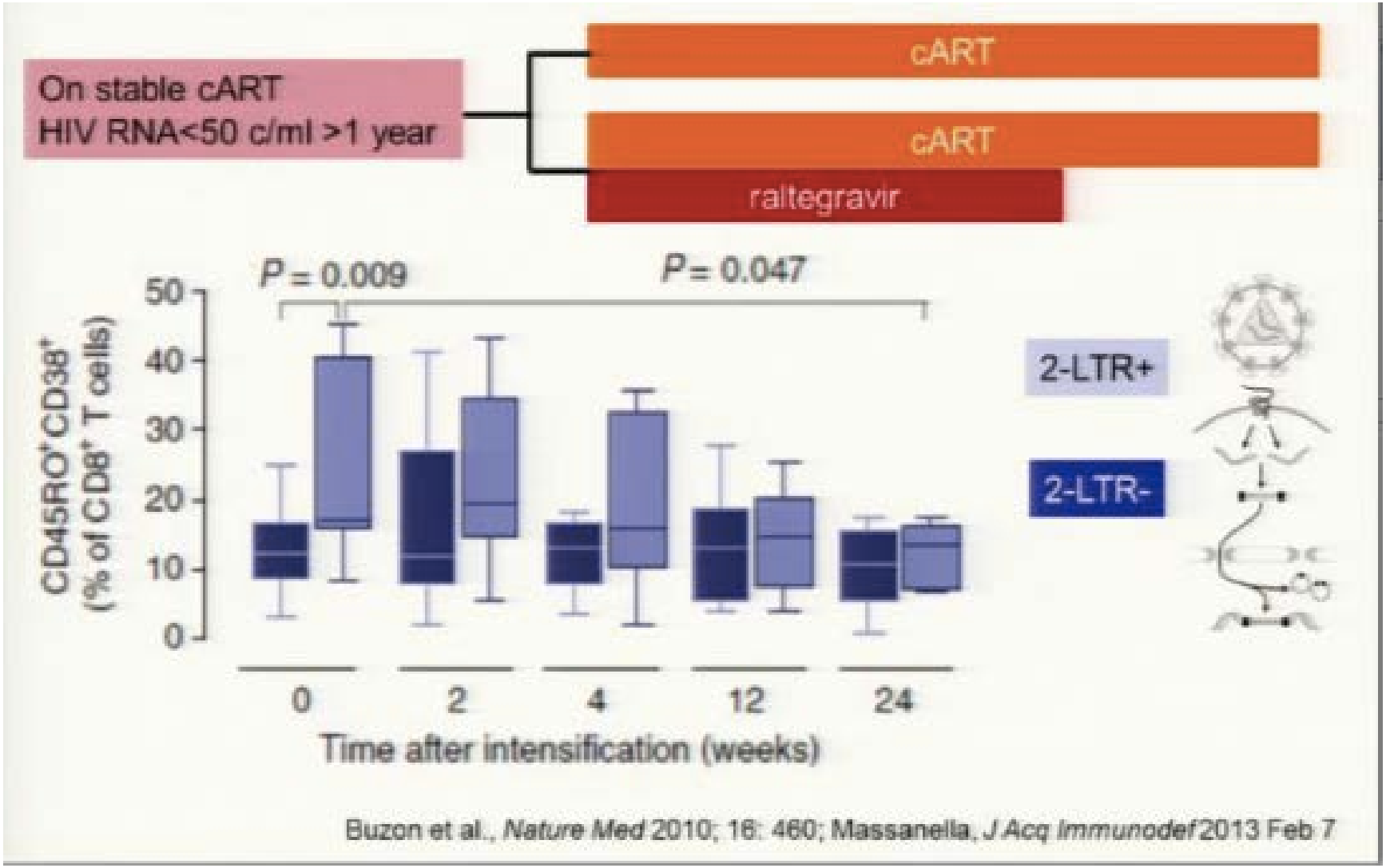


With ongoing replication, integrase inhibitors may increase the levels of episomal, 2-LTR circle DNA

No impact on total and integrated DNA

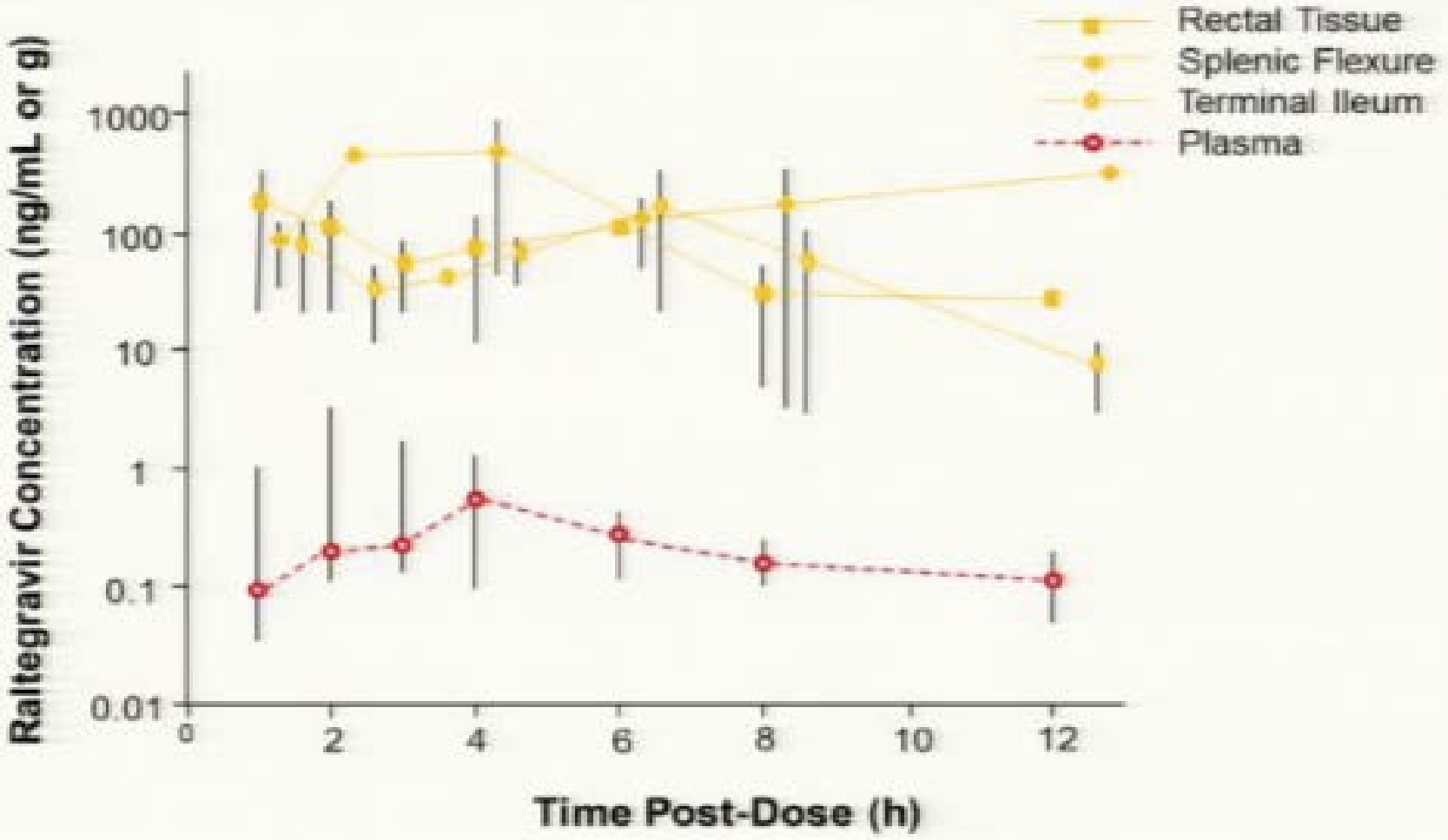
NATURE MEDICINE VOLUME 16 | NUMBER 4 | APRIL 2010

Raltegravir reduced T cell activation



Buzon et al., *Nature Med* 2010; 16: 460; Massanella, *J Acq Immunodef* 2013 Feb 7

Very high Raltegravir level in digestive tissue



Patterson et al., AIDS 2013:27

Increase in 2-LTR Circles After Raltegravir Intensification in HAART-Suppressed Patients with High CD4+ T Cell Counts: A Randomized, Placebo-Controlled Trial

H Hatano[1], M Strain[2], R Scherzer[1], E Sinclair[1], S Palmer[3], M Busch[1,4], P Bacchetti[1], P Hsue[1], D Richman[2], S Deeks[1]

[1] University of California, San Francisco, CA, USA

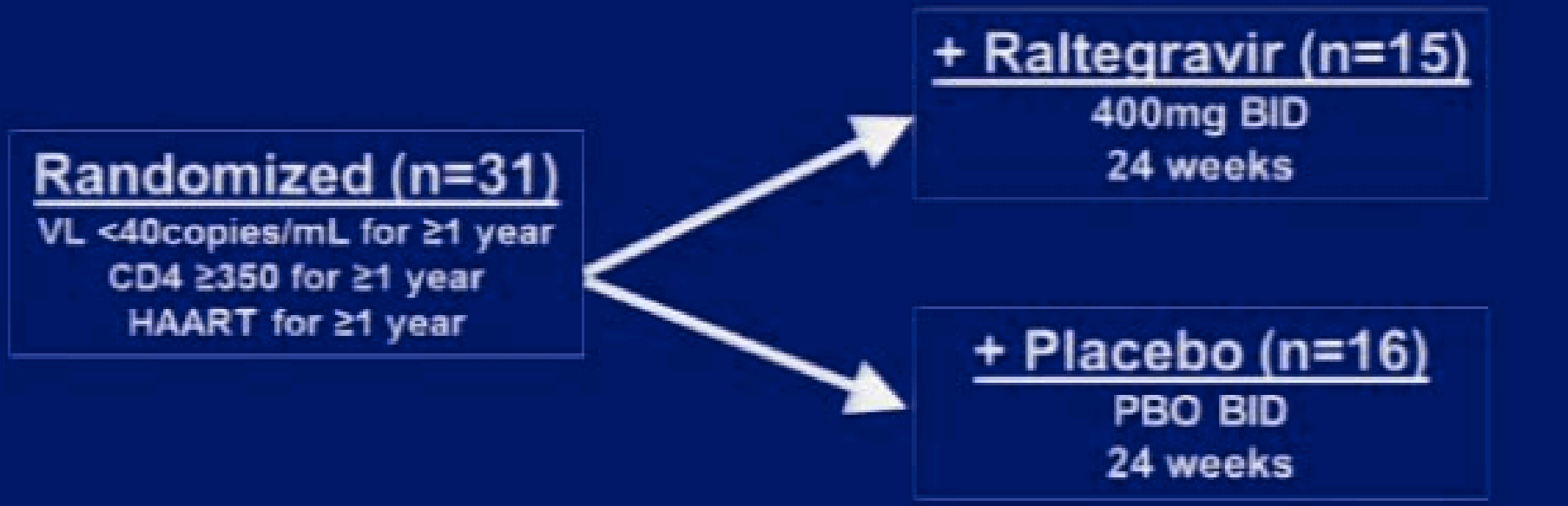
[2] University of California, San Diego, CA, and VA San Diego Healthcare System, San Diego, CA, USA

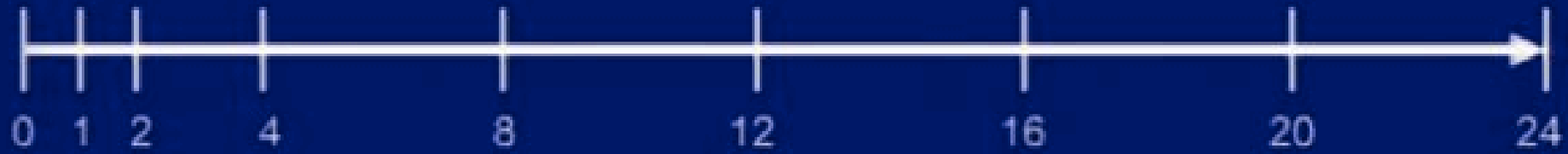
[3] Karolinska Institutet, Solna, Sweden

[4] Blood Systems Research Institute, San Francisco, CA, USA

ClinicalTrials.gov NCT00843713

Study Design

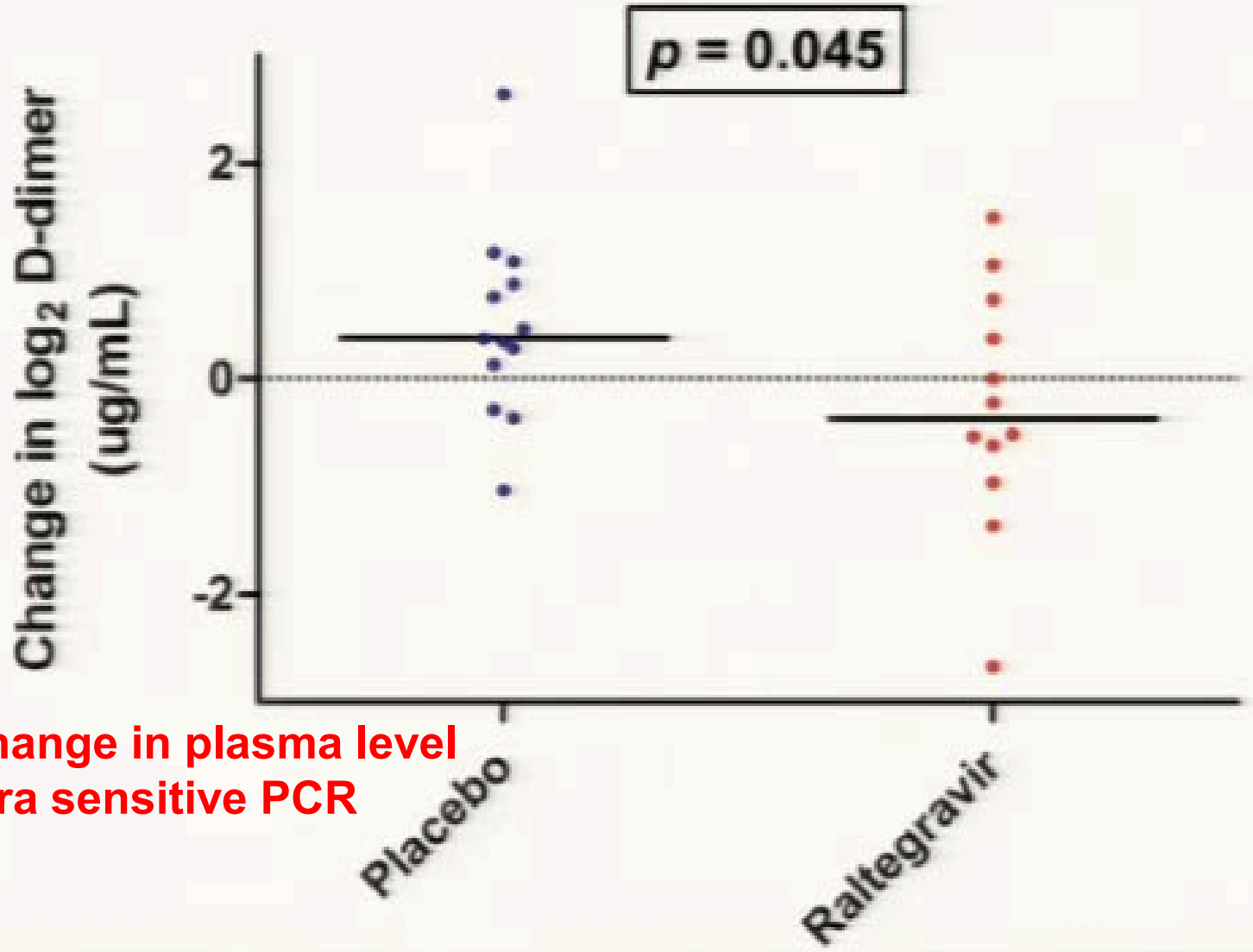




Increase in 2-LTR Circles in Raltegravir Group Compared to Baseline

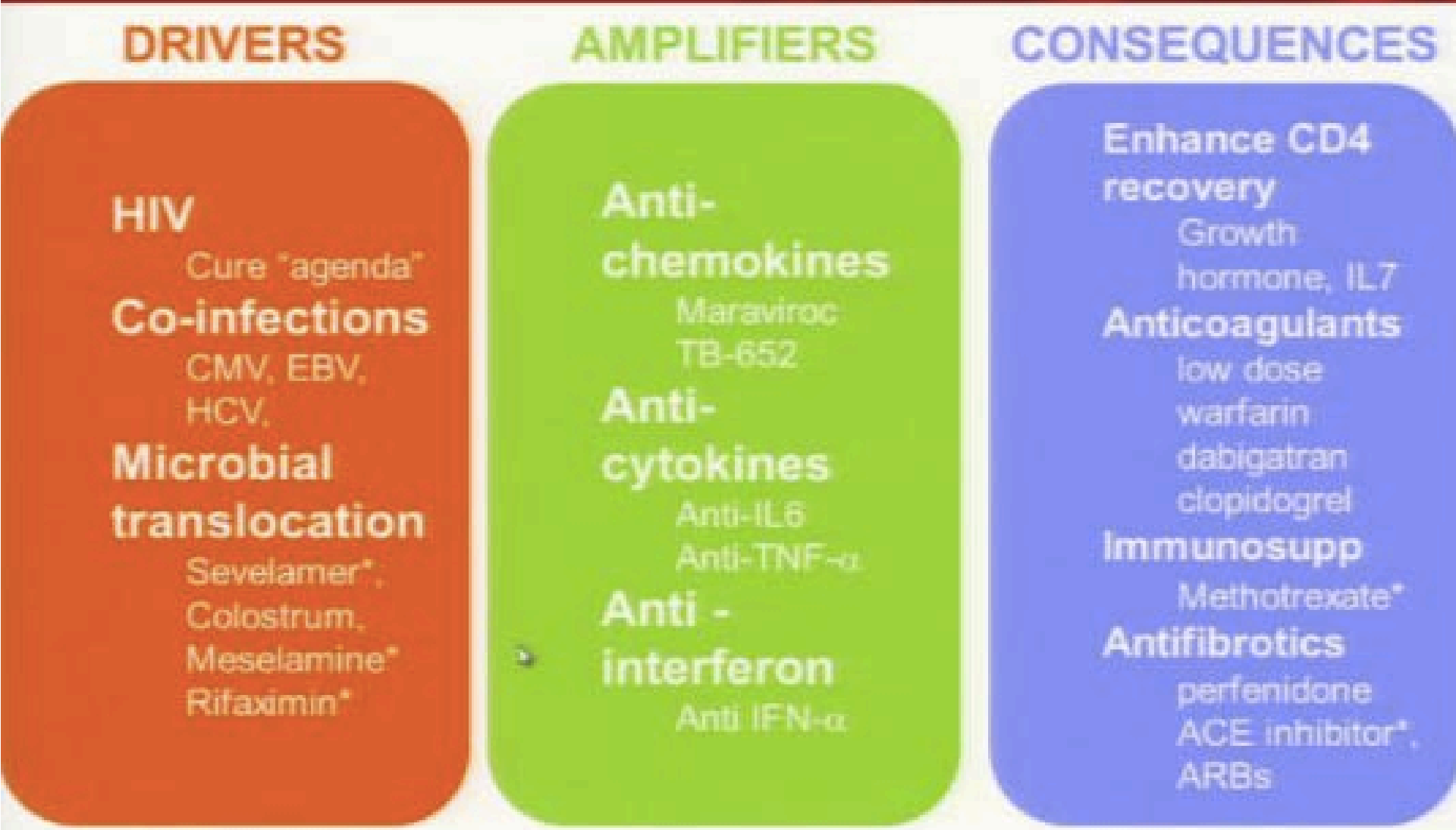
- RGV group had a significant increase in 2-LTR circles compared to baseline
  - Ratio of week 1 to 0: 4.7 (p=0.0045)
  - Ratio of week 2 to 0: 3.4 (p=0.046)
  - Ratio of week 8 to 0: 3.6 (p=0.033)
- No substantial changes in 2-LTR circles in PBO group

Raltegravir Intensification Led to Significant Decrease in D-dimer



No change in plasma level of ultra sensitive PCR

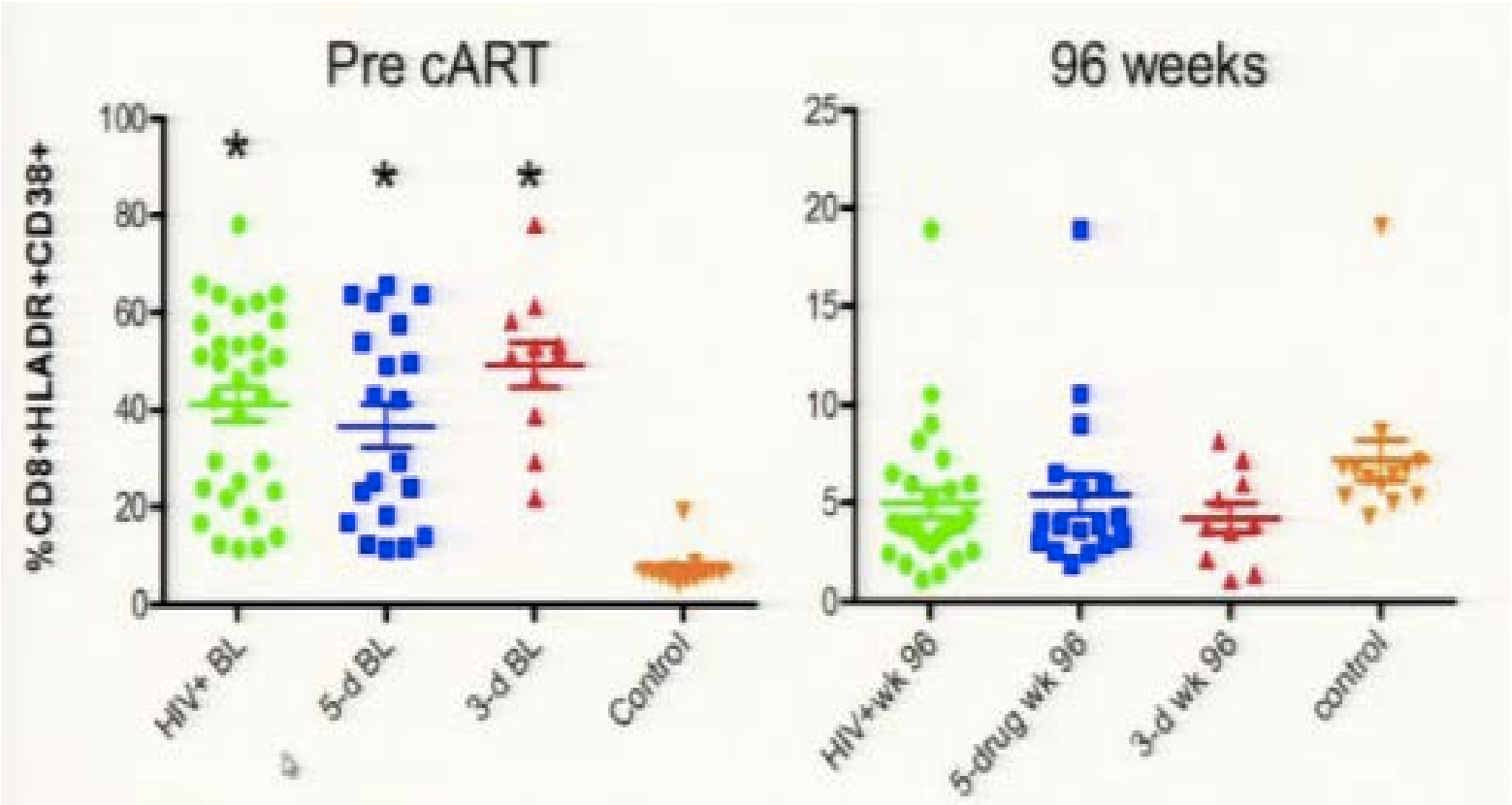
Therapeutics in development



* Registered on clinicaltrials.gov

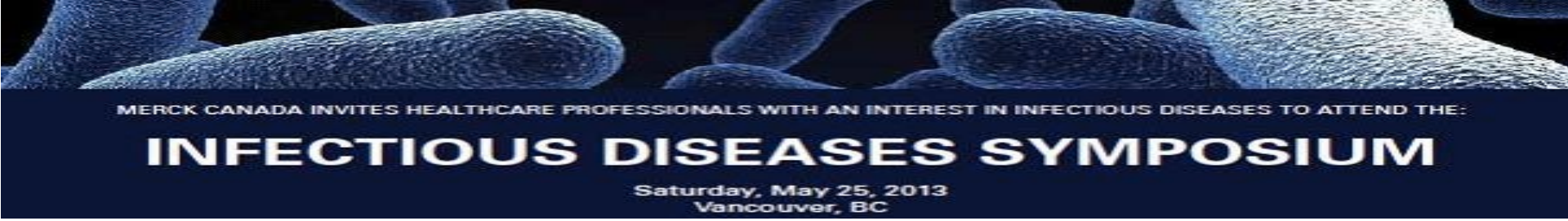
Lewin S : HIV and inflammation CROI 2013

Early ART reduced inflammation



n=31 treated during acute infection. 5 drugs (n=20); 3 drugs (n=11)
Mean (range) duration of infection 42 (19-155) days
* $p<0.05$

Markowitz et al, 19th IAC, Washington DC, July 2012



Conclusion

- Monocytes inflammation emerging as a new contributor for CV
- Raltegravir reduces HIV-inflammation:
  - Lipid friendly
  - Reduction of inflammation
  - Class effect: data pending
- Early ART remains the best way to control inflammation

Réseau SIDA/MI du FRSQ

“The Berlin patient”

The New York Times

April 30, 2013

Heidi Schumann for The New York Times

Timothy Ray Brown, widely known as the Berlin patient, was effectively cured of AIDS in 2006. He had two very risky bone marrow transplants to treat leukemia and doctors believe that a special mutation in the donor's tissue conferred immunity to Mr. Brown.


AIDS
IS GOING TO
LOSE.