Jornadas 2012

Actualizaciyn en Atenciyn Farmacйutica al Paciente Con Patologнas Vнricas

Hacia la Curación del VIH

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HIV can be eradicated

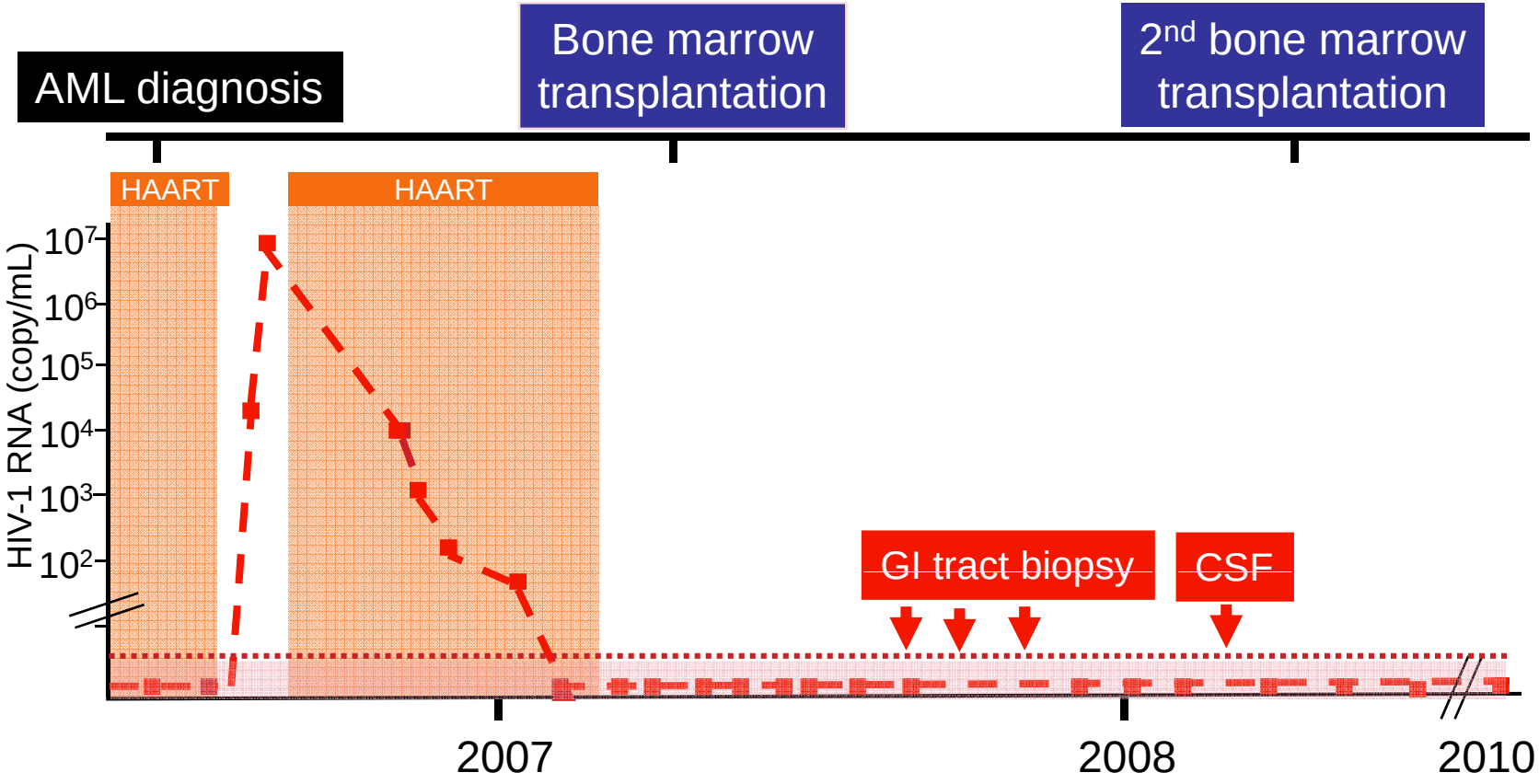
BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

Hutter G, *et al. N Engl J Med* 2009;**360**:692-8

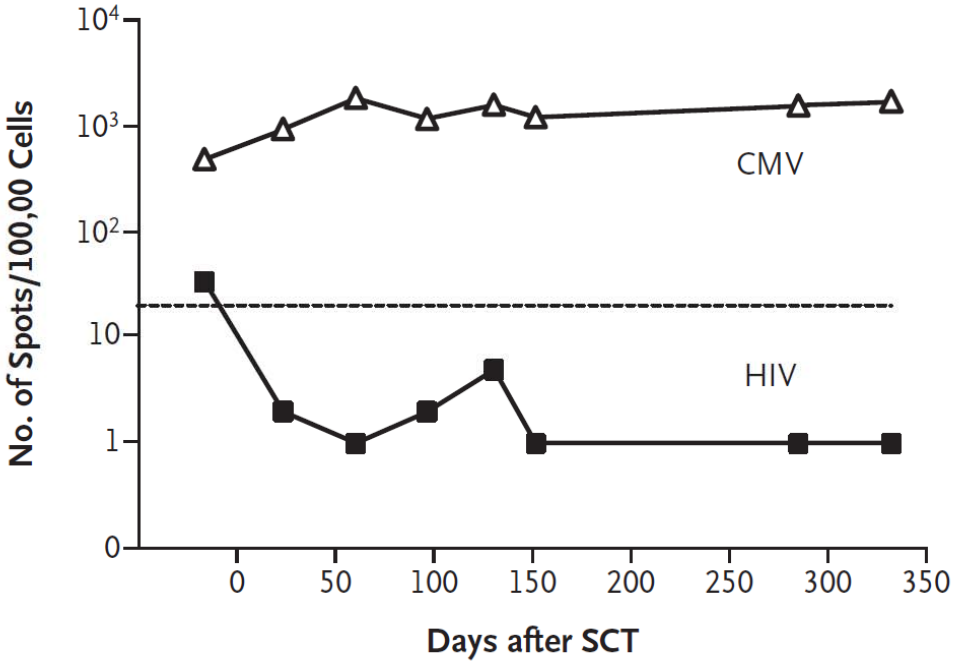
Sterilising cure: lessons learned

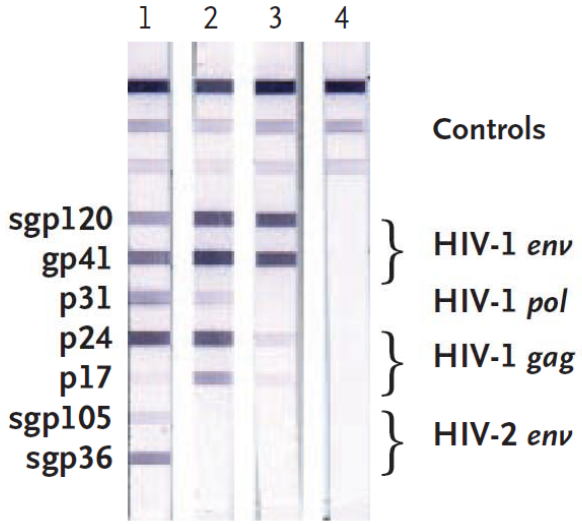


- Latently infected cells can be eliminated
- Anatomical reservoirs can decay
- Complete viral suppression without HAART is possible

Adapted from Hutter G, *et al. N Engl J Med* 2009;**360**:692-8

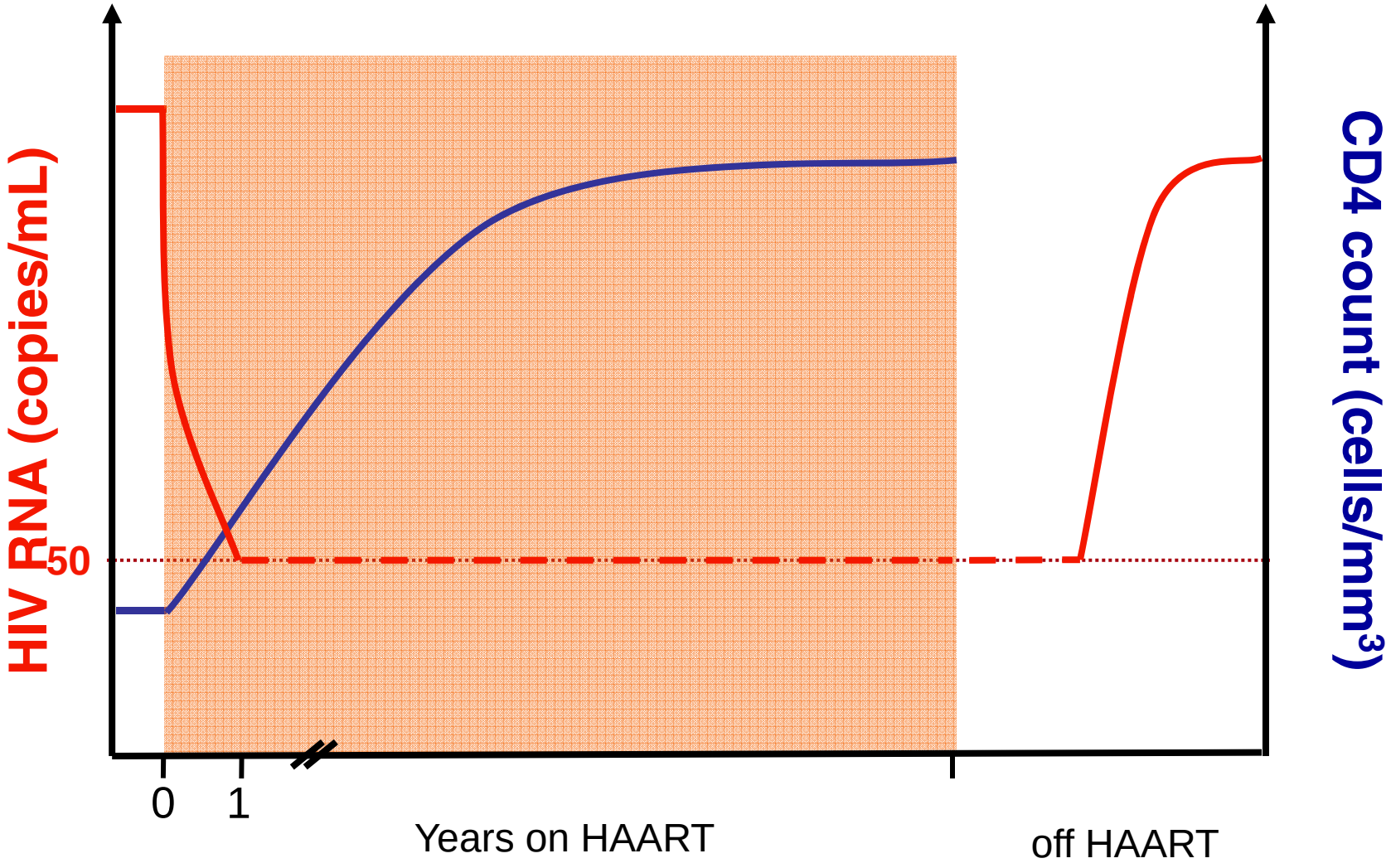
Cellular and humoral response to HIV-1





Adapted from Hutter G, *et al. N Engl J Med* 2009;**360**:692-8

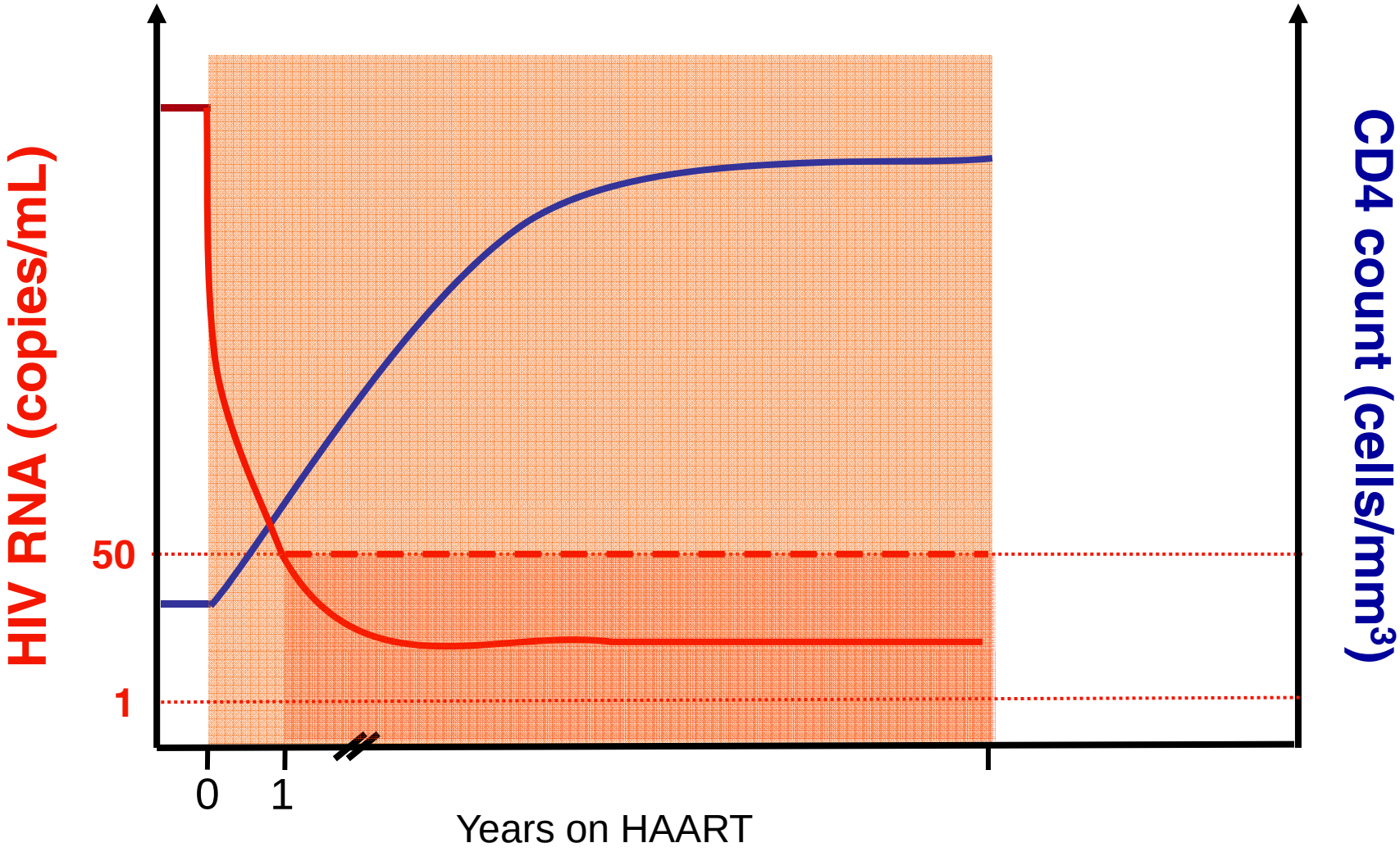
Why is HIV not eradicable?
Rapid rebound when HAART stopped



Where does HIV come from?

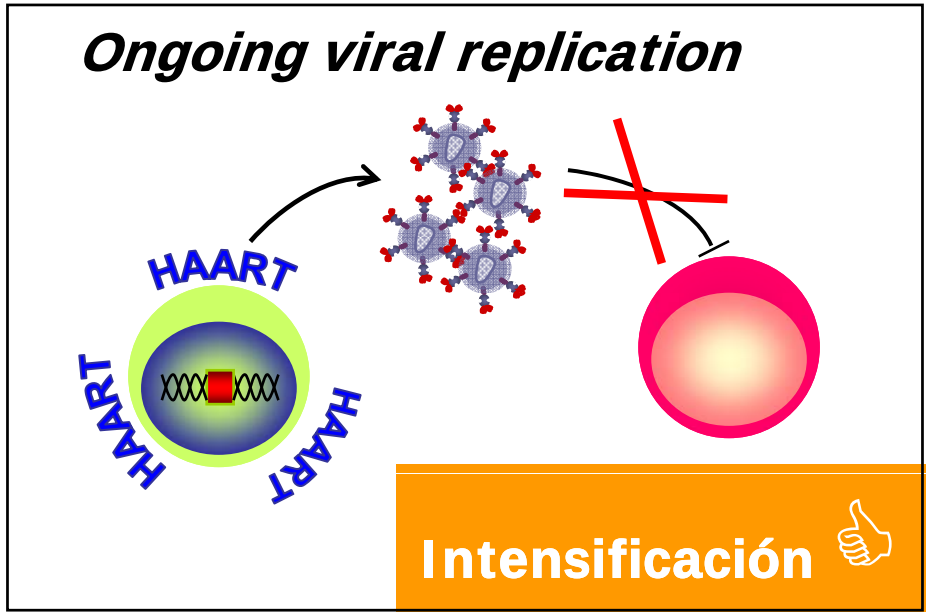
- Residual replication
- Cell reservoirs (latently infected T cells)
- Anatomical reservoirs

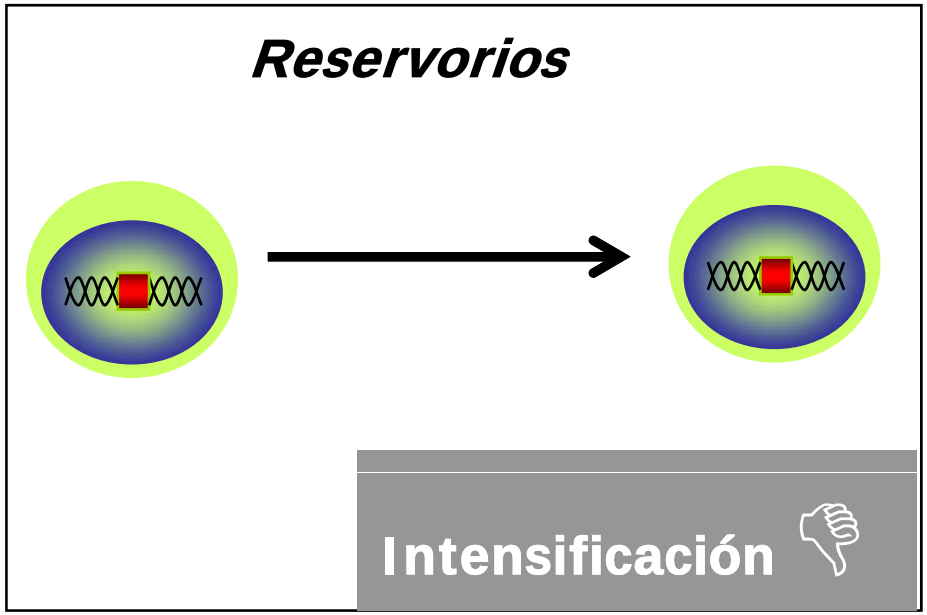
Is there residual replication? Plasma



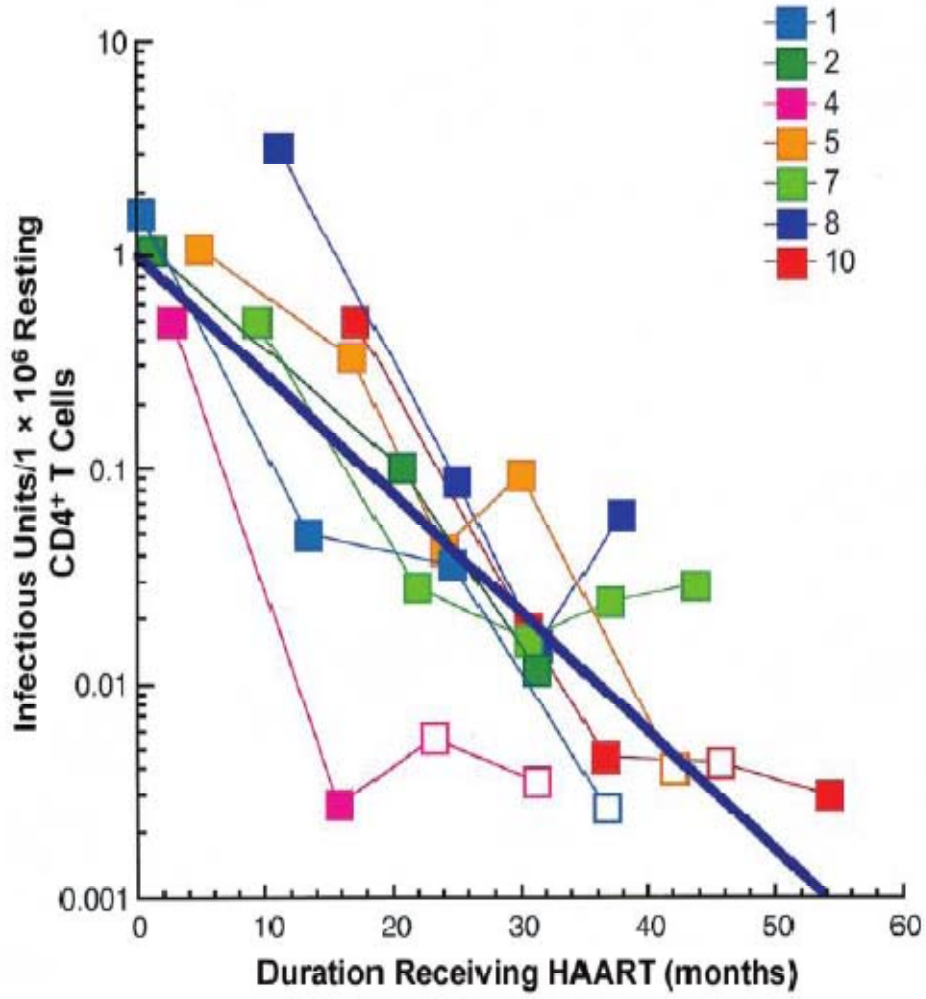
Palmer S, *et al. Proc Natl Acad Sci USA* 2008;**105**:3879-84.
Maldarelli F, *et al. Plos Pathog* 2007;**3(4)**:e46.

Estrategias para erradicación de VIH: Intensificación



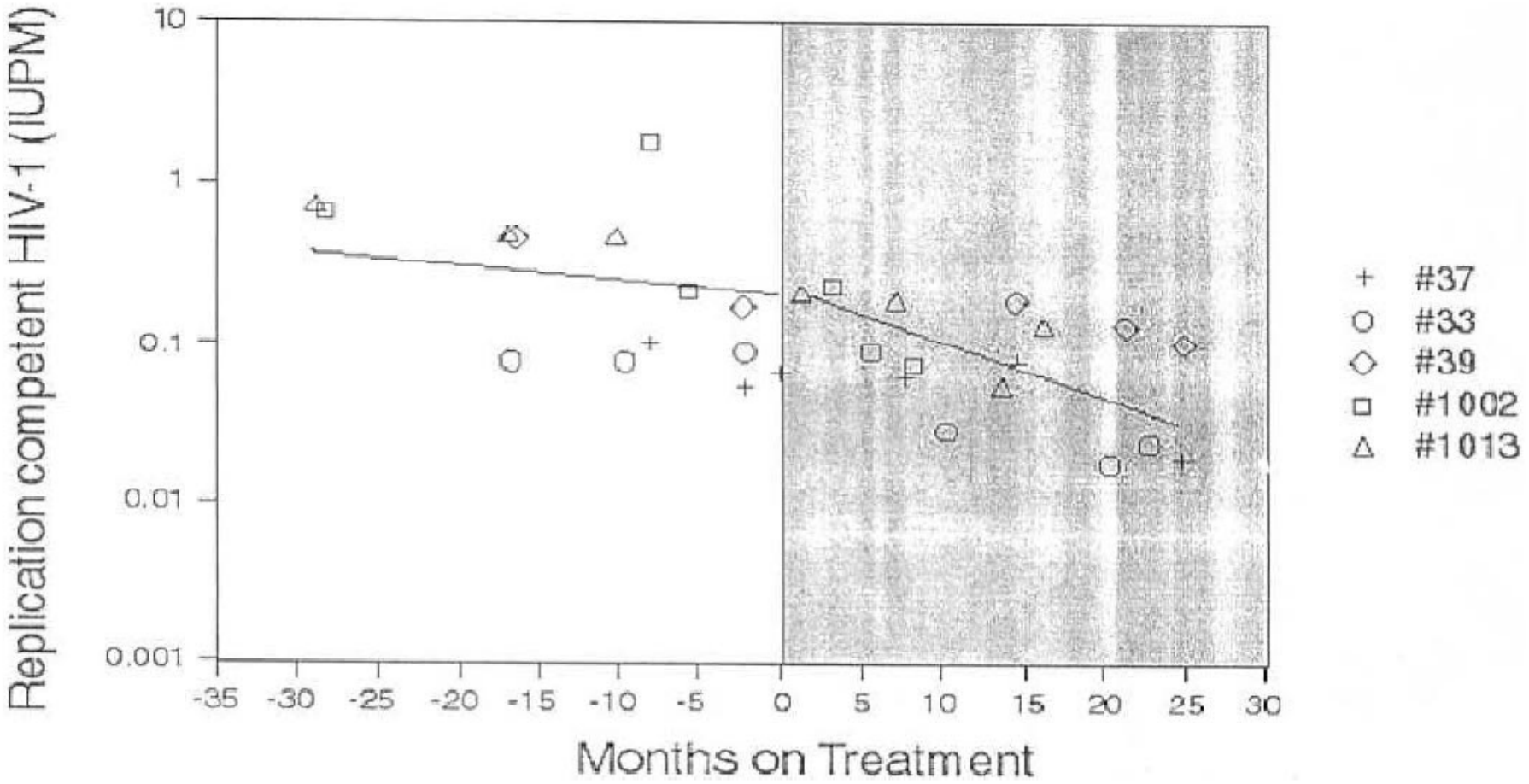


Acutely Infected Patients



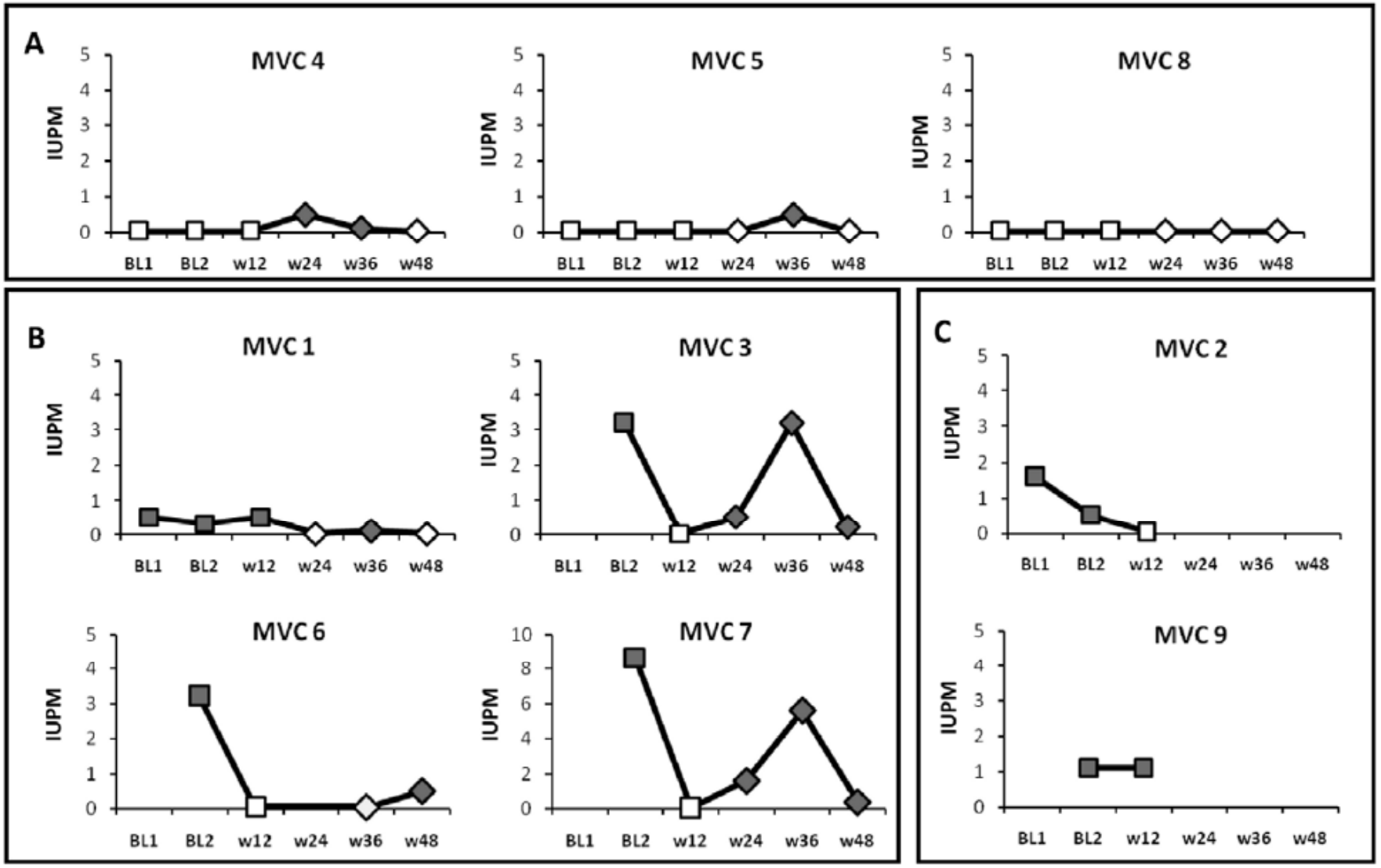
Chun TW, et al. J Infect Dis 2007;195:1762-4

Intensification with ABC±EFV



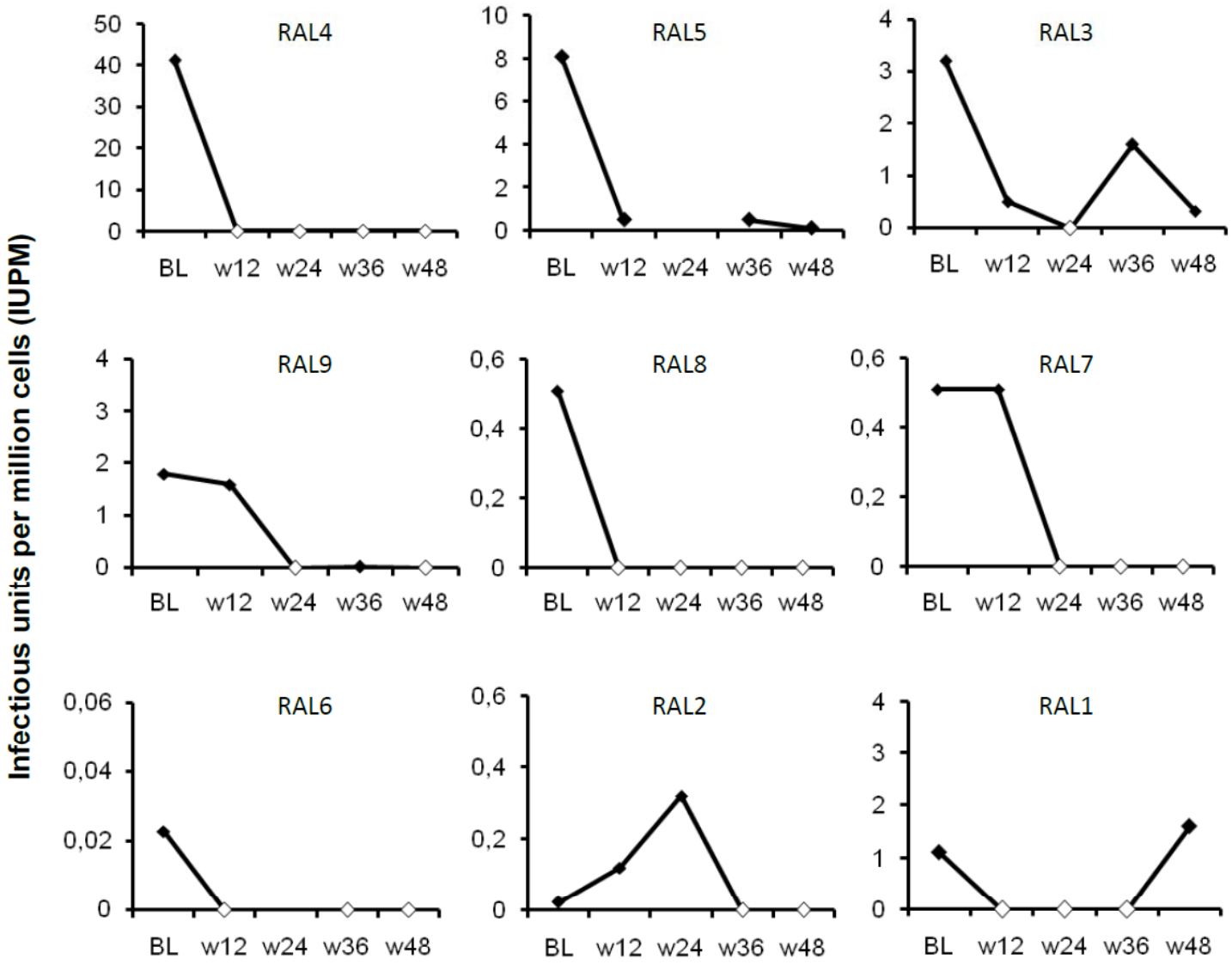
Ramratnan B. J AIDS 2004

Intensification with Maraviroc



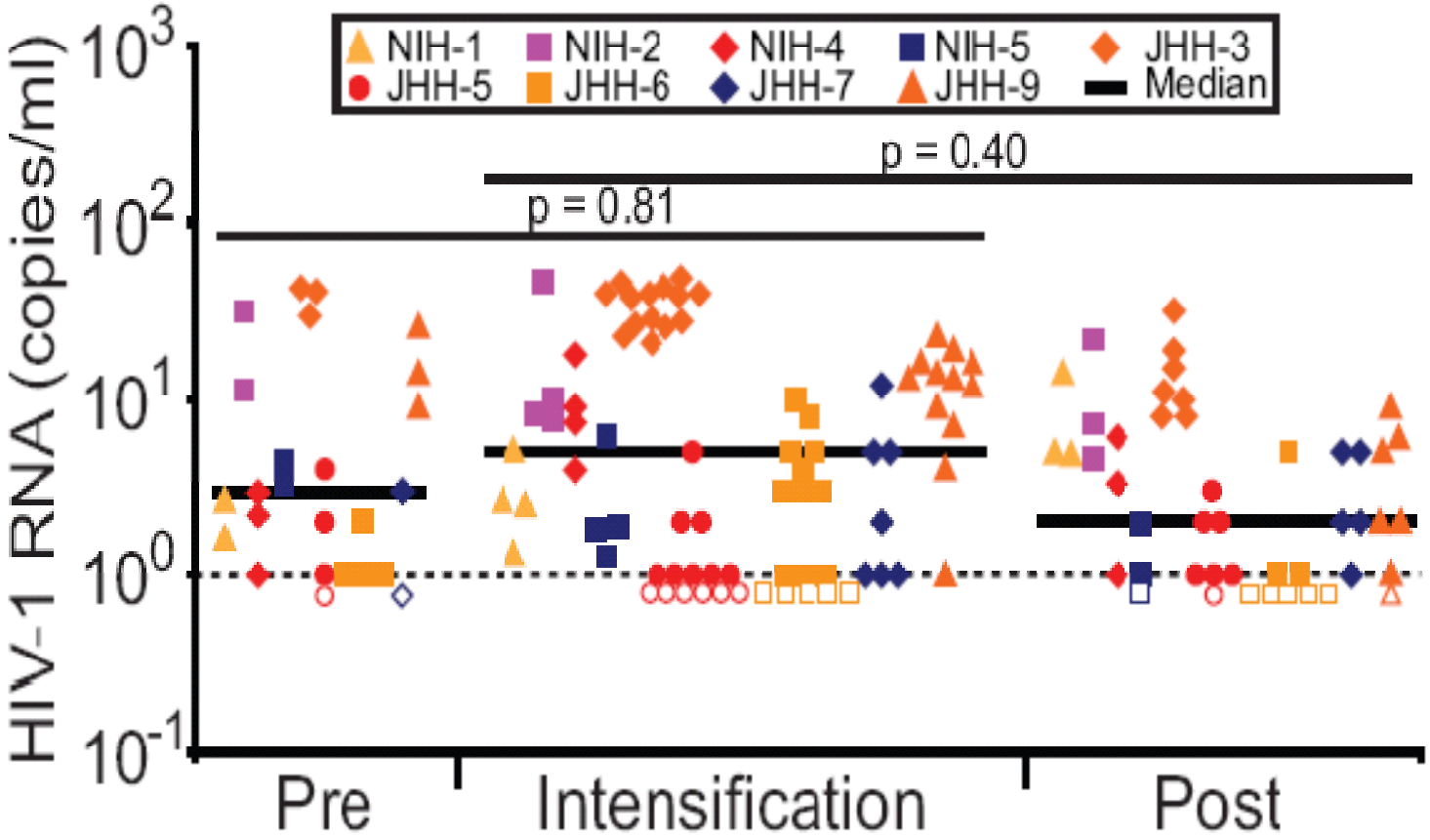
Gutierrez C. PLoS One 2011

Intensification with Raltegravir



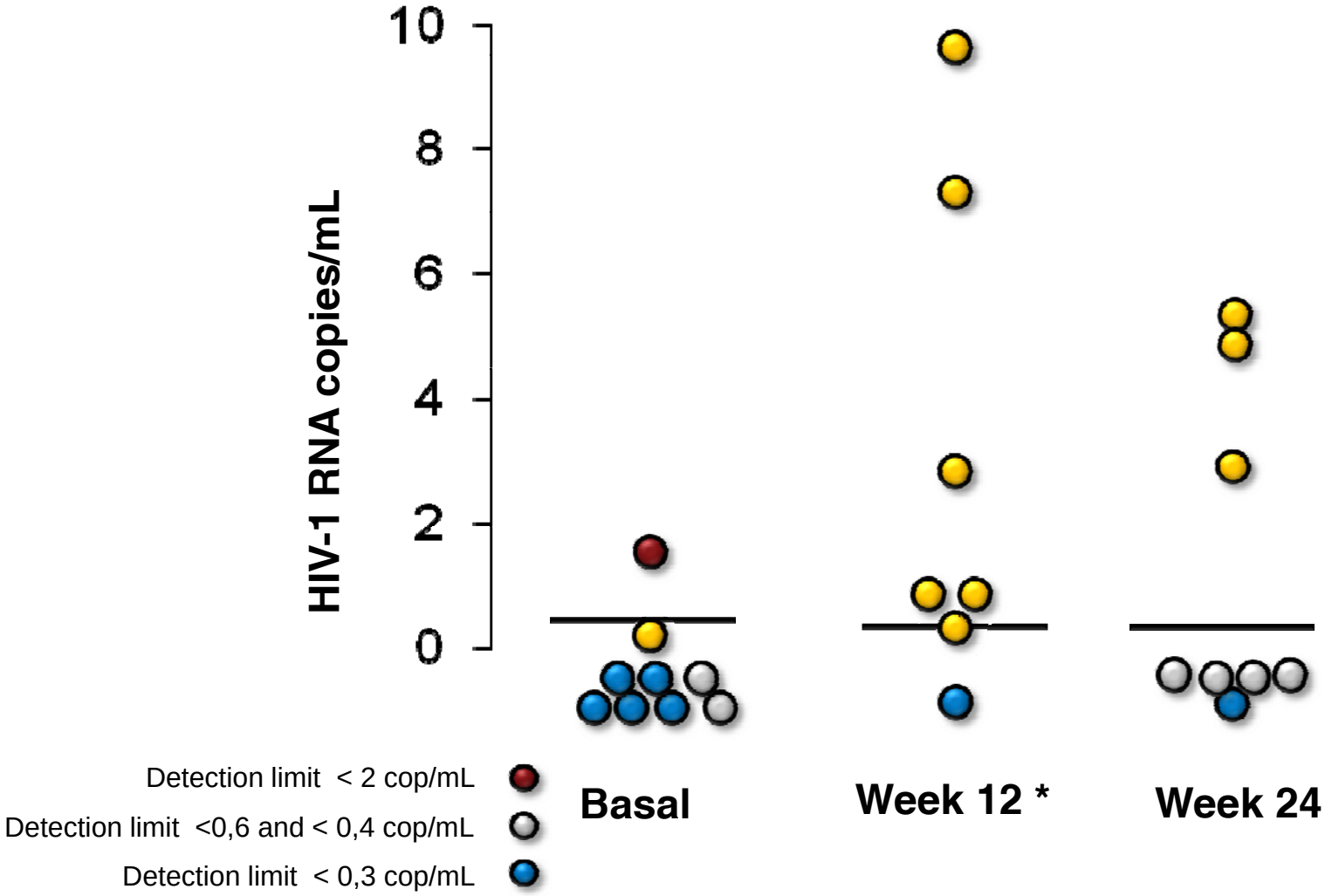
Vallejo A (submitted)

ART intensification with PI or EFV does not reduce residual viraemia



Dinoso JB, *et al. Proc Natl Acad Sci USA* 2009;**106**:9403-8.

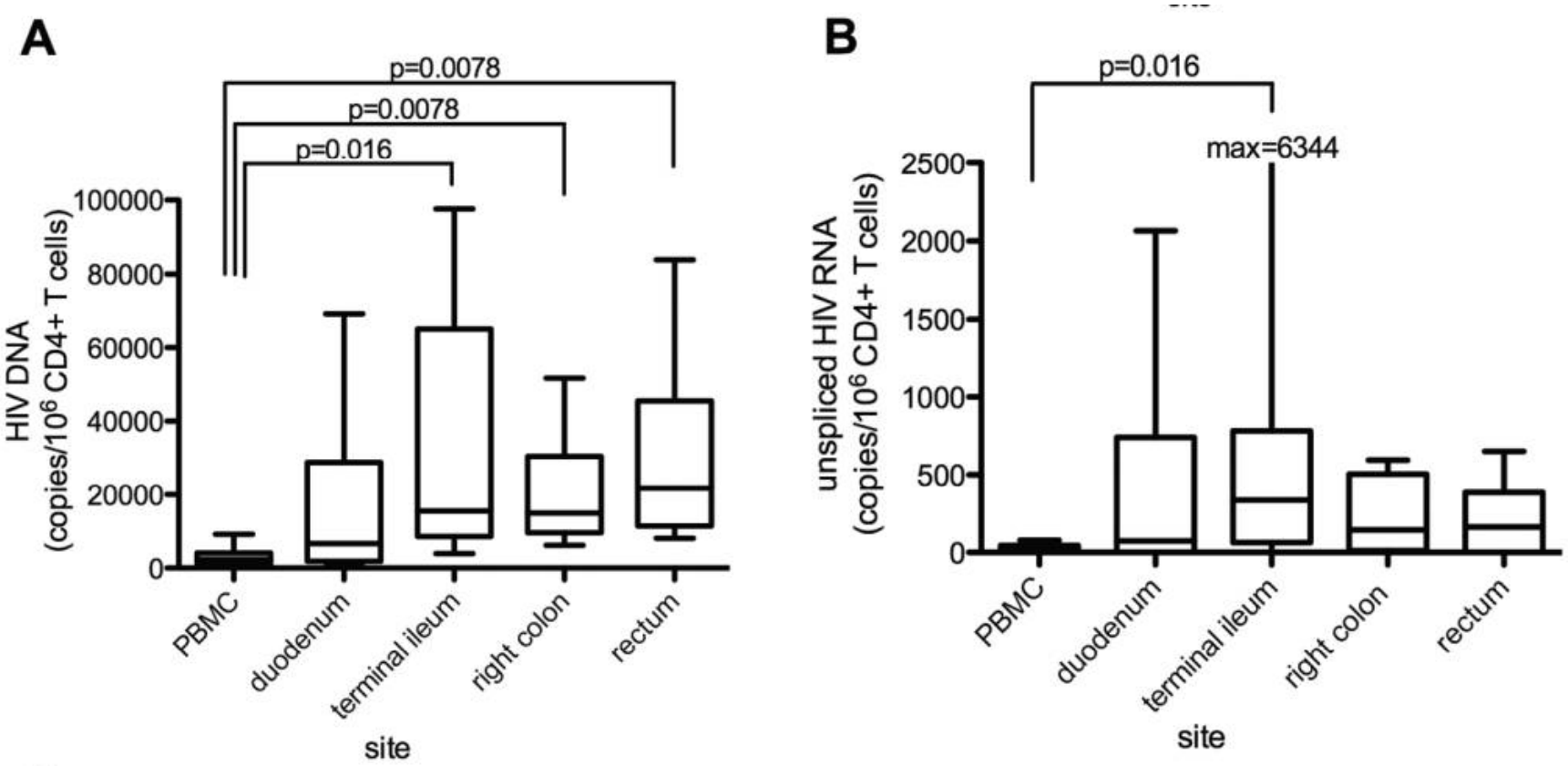
ART intensification with maraviroc does not reduce residual viraemia



Gutiérrez C, *et al*. XXVIII International AIDS Conference, *Vienna* 2010 TUPE0015.

* **Failure of internal standard in 2 samples**

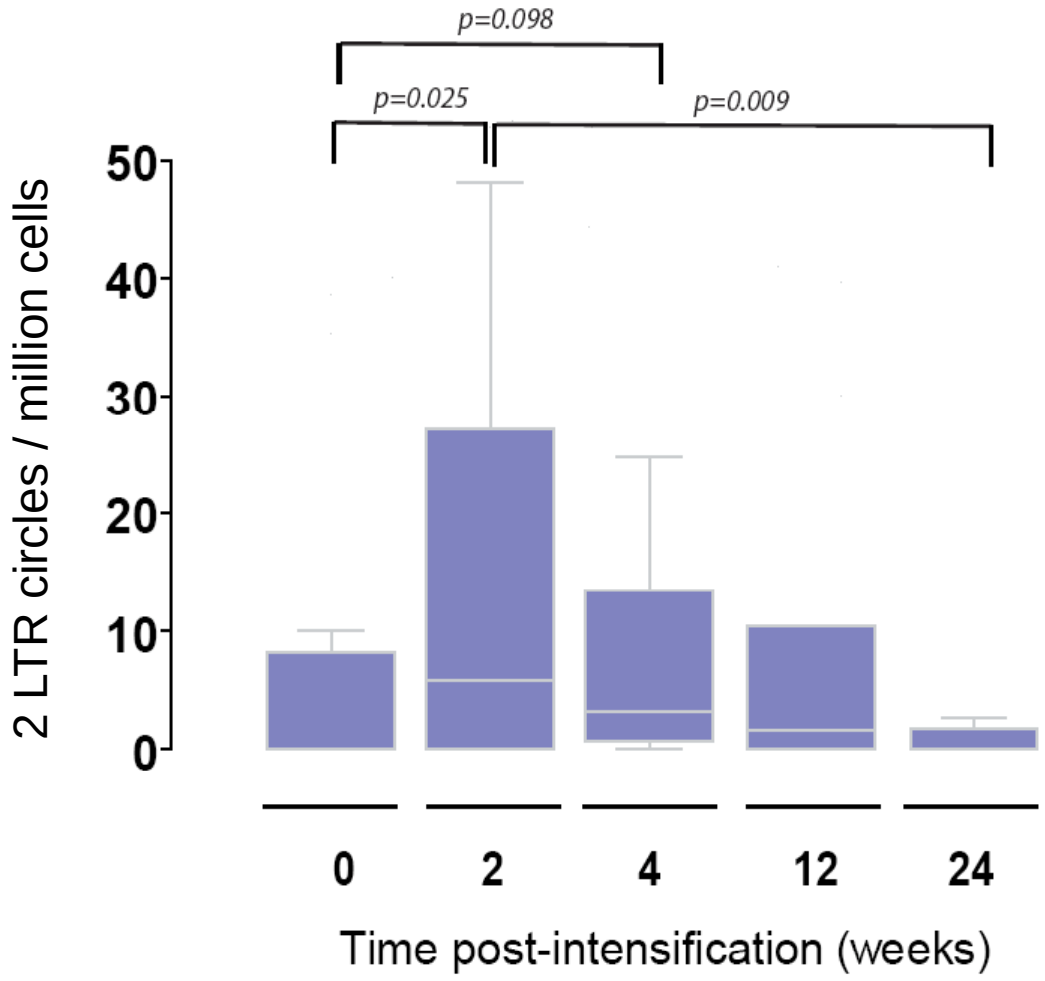
Is there residual HIV replication? GI tract

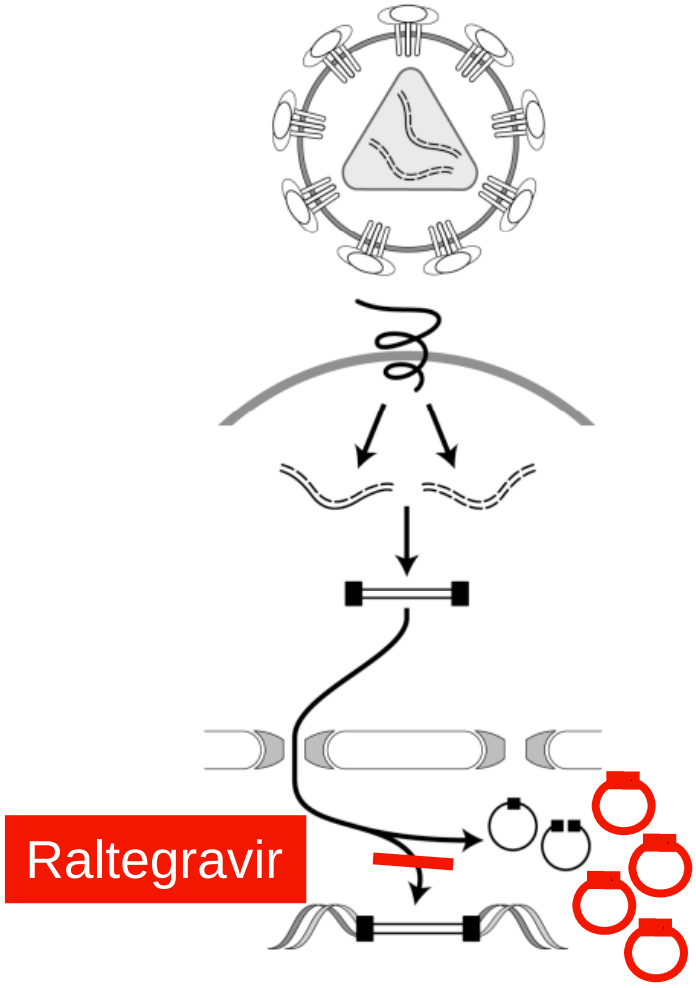


N=8, time on HAART with undetectable HIV RNA 2.8 – 12 years

Adapted from Yukl SA, *et al*. *J Infect Dis*. 2010;202:1553-61.

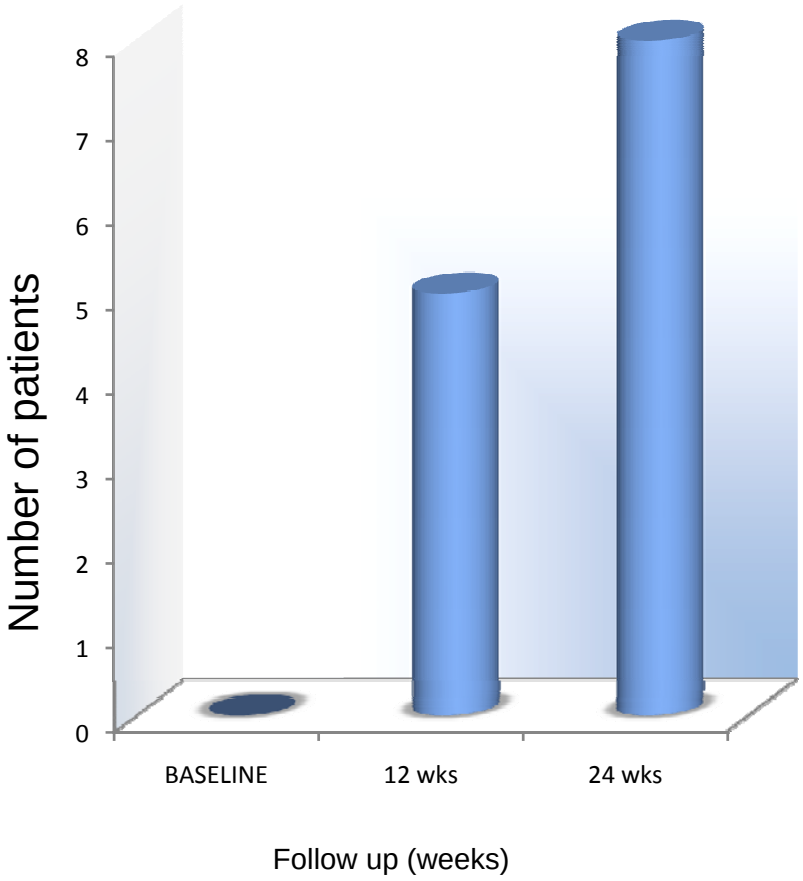
Raltegravir intensification: one third of patients have residual replication

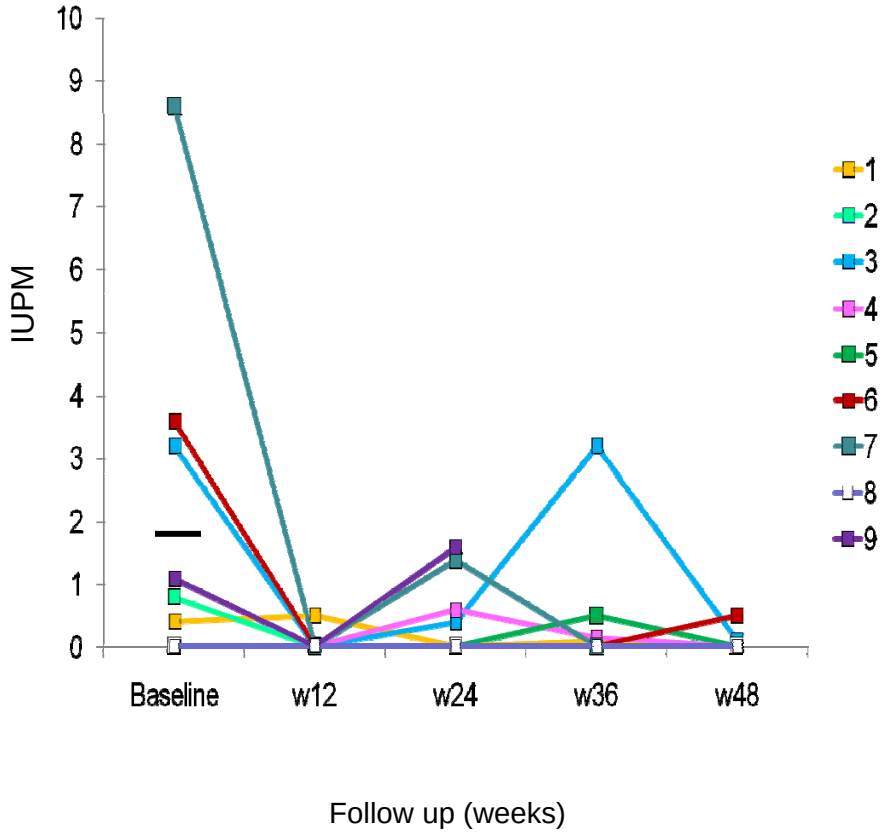




Adapted from Buzón MJ, *et al. Nat Med* 2010;16: 460-5.

MVC intensification: increased 2LTR circles and decreased cell reservoir



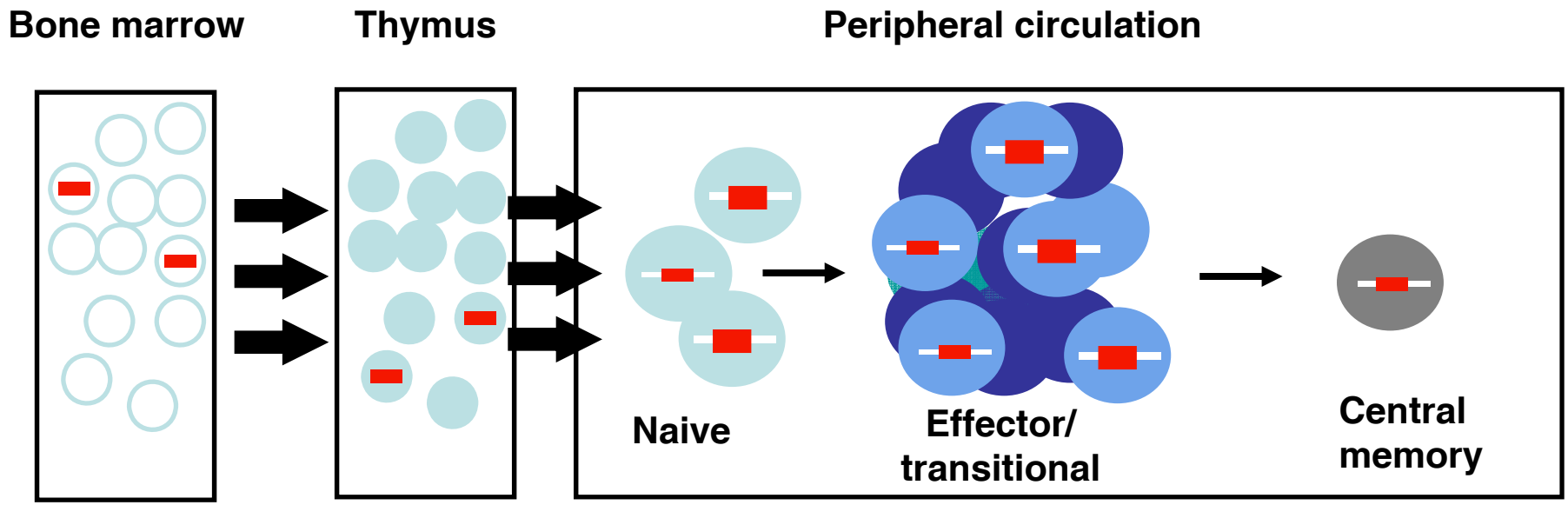


Gutiérrez et al., XXVIII International AIDS Conference, *Vienna* 2010 TUPE0015.

Barriers to cure: Residual viral replication

- It seems unlikely that viral replication occurs in plasma in patients on ART
- It seems very likely that viral replication occurs in extraplasma sites (i.e. gut) in patients on ART
- The need to intensify therapy for eradication purposes still to be answered, but possibly a cure will not be achievable without suppressing all residual viral replication in tissues
- Important not to confuse with the immediate clinical benefits of intensification (*none!*)

The cell reservoir: latent infection can be established in many T cells

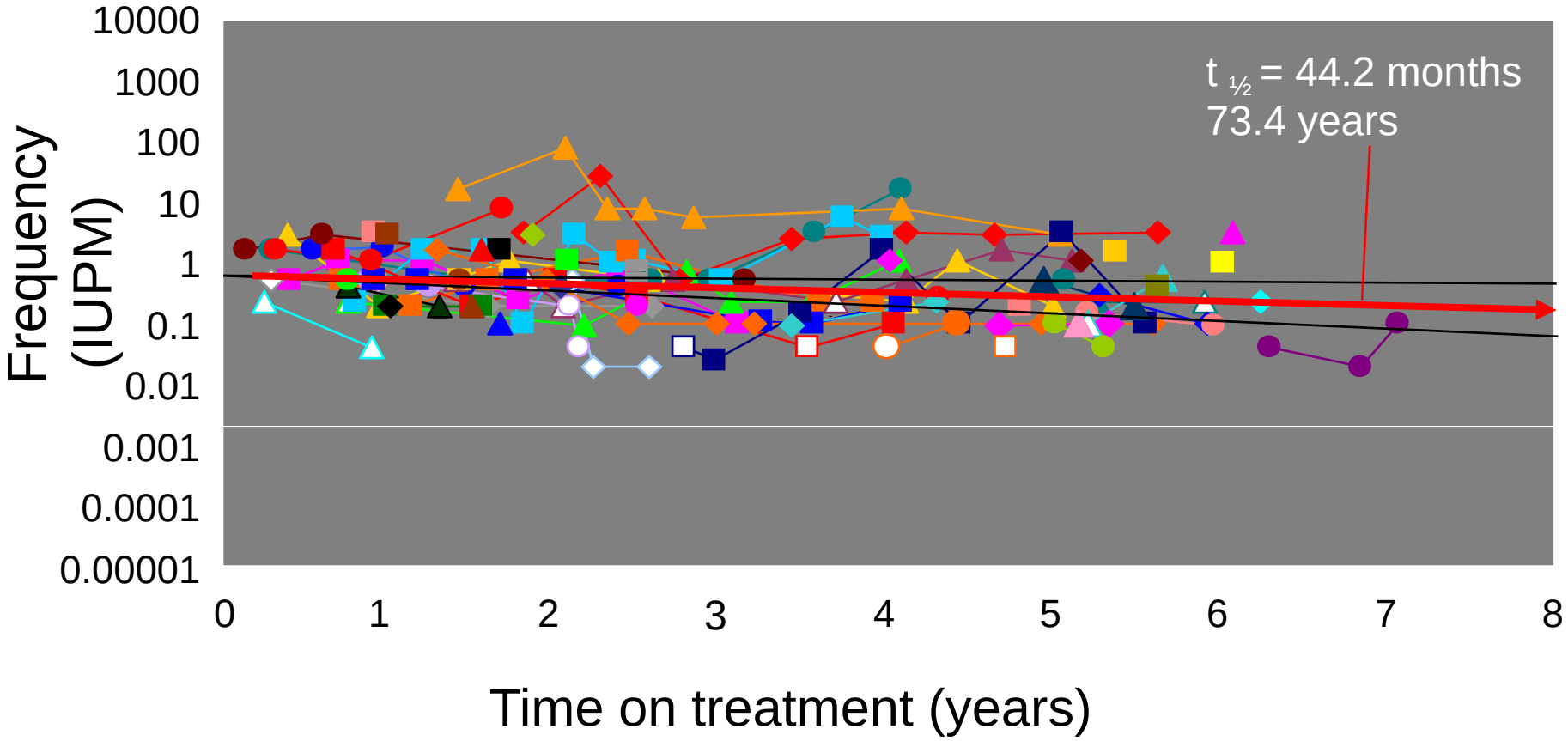


Multipotent progenitor cells → Naïve T cells → Transitional memory → Central memory

Latent reservoir

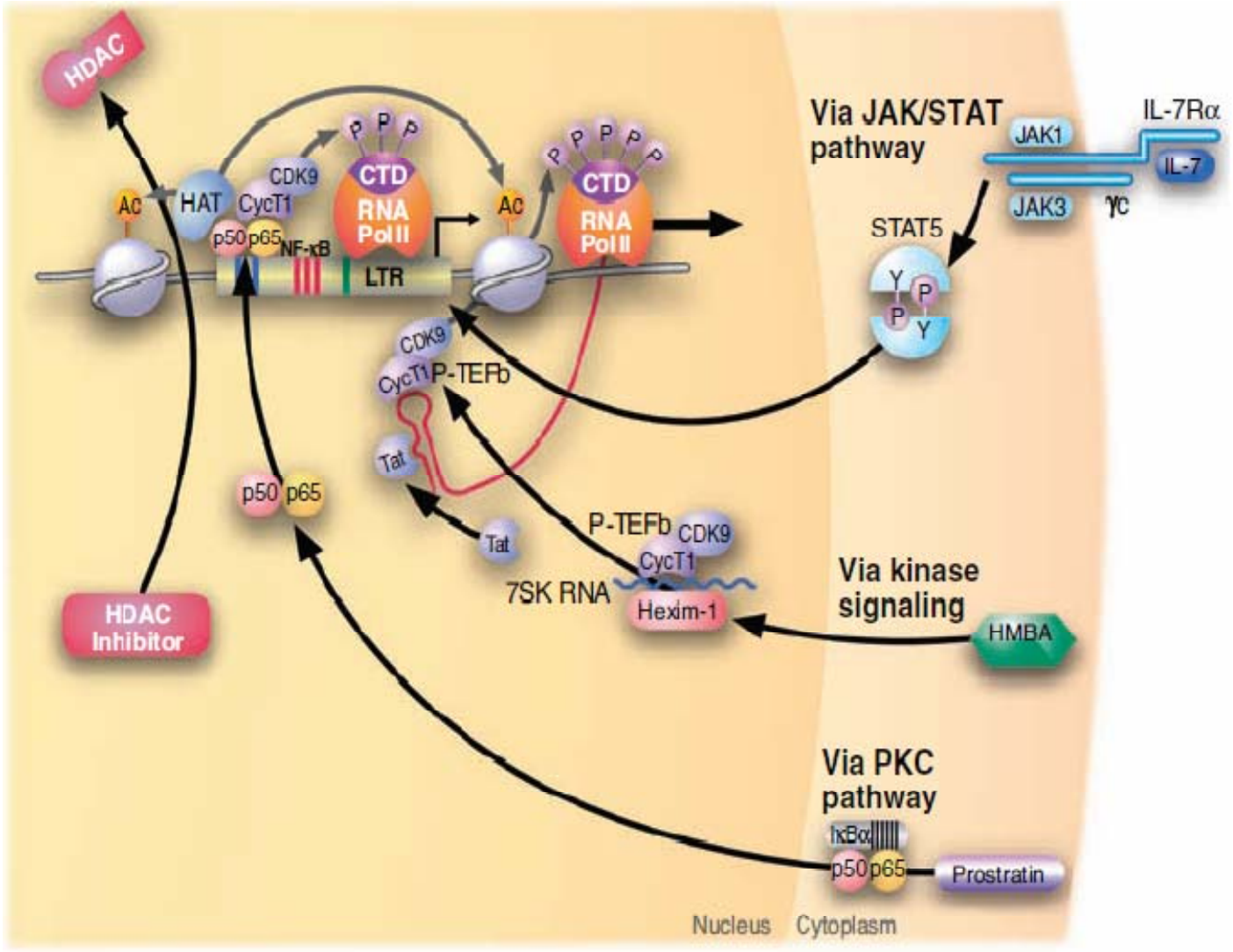
Chun TW, *et al. Nature* 1997*;* **387**:183-8; Finzi D, *et al. Science* 1997;**278**:1295-300; Brooks DG, *et al. Nat Med* 2001;**7**:459-64; Chomont N, *et al. Nat Med* 2009;**15**:893-900; Dai J, *et al.* J Virol 2009: **83**:4528-37; Carter CC, *et al. Nat Med* 2010;**16**:446-51; Wightman F, *et al. J Infect Dis* 2010;**202**:1738-48.

Stability of latently infected T cells



Adapted from Siliciano JD, *et al. Nat Med 2003;***9:**727-8.

Potential anti-latency drugs



Adapted from Richman DD, *et al. Science* 2009;**323**:1304-7

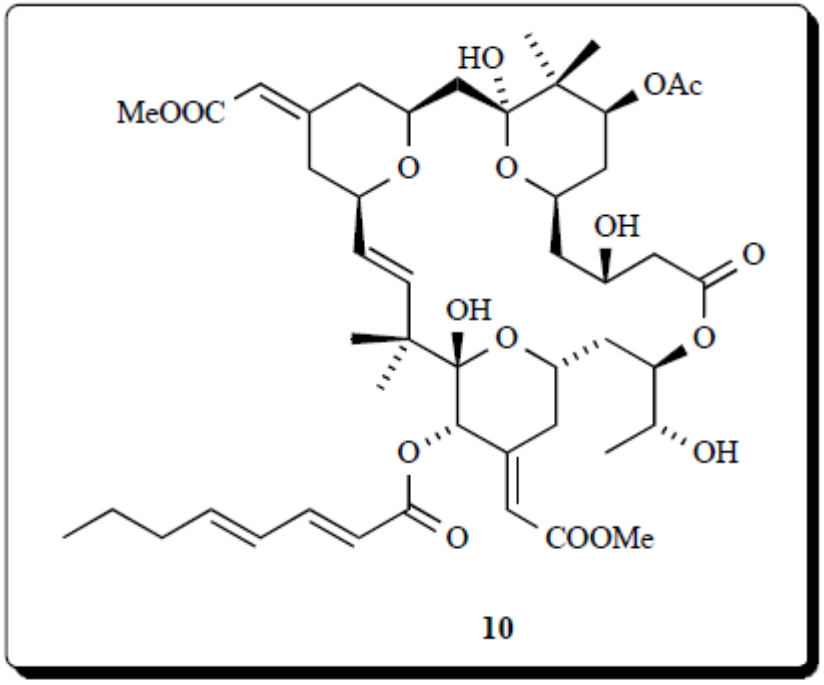
Drugs under investigation

- Histone deacetylase inhibitors
  - >25 HDACis in advanced clinical development for cancer
  - Vorinostat (SAHA; Merck) licensed for T-cell lymphoma
- PKC agonists
  - Prostratin, Bryostatin-1
- Combination therapy most potent

Bolden JE, *et al. Nat Rev Drug Disc* 2006;**5**:769-84; Prince HM, *et al. Clin Cancer Res* 2009;**15**:3958-69; Contreras X, *et al. J Biol Chem* 2009;**284**:6782-9; Archin NM, *et al. AIDS Res Hum Retroviruses* 2009;**25**:207-12; Reuse S, *et al. PLos One* 2009;**4**:e6093; Burnett JC, *et al. J Virol* 2010:**84**:5958-74

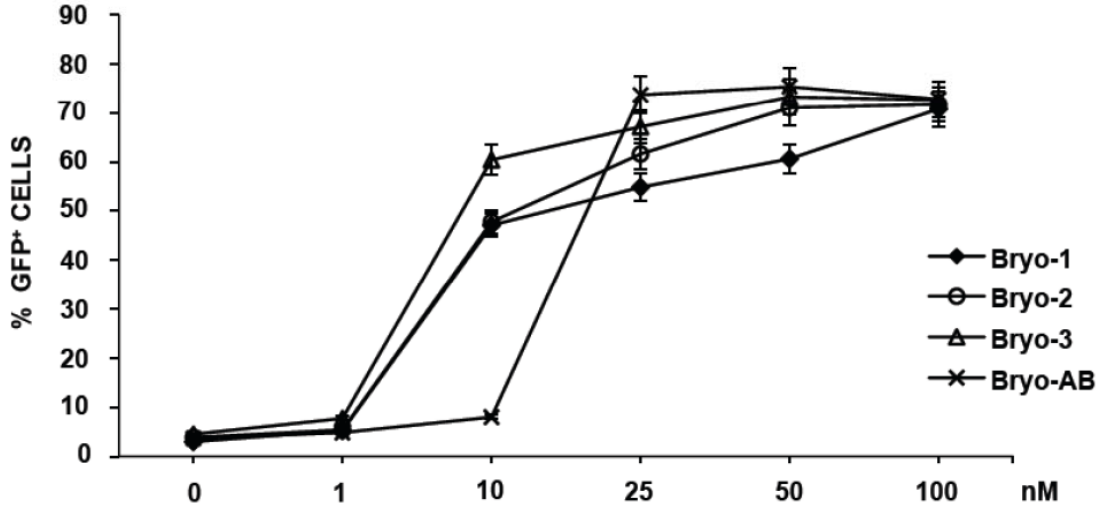
Bryostatin

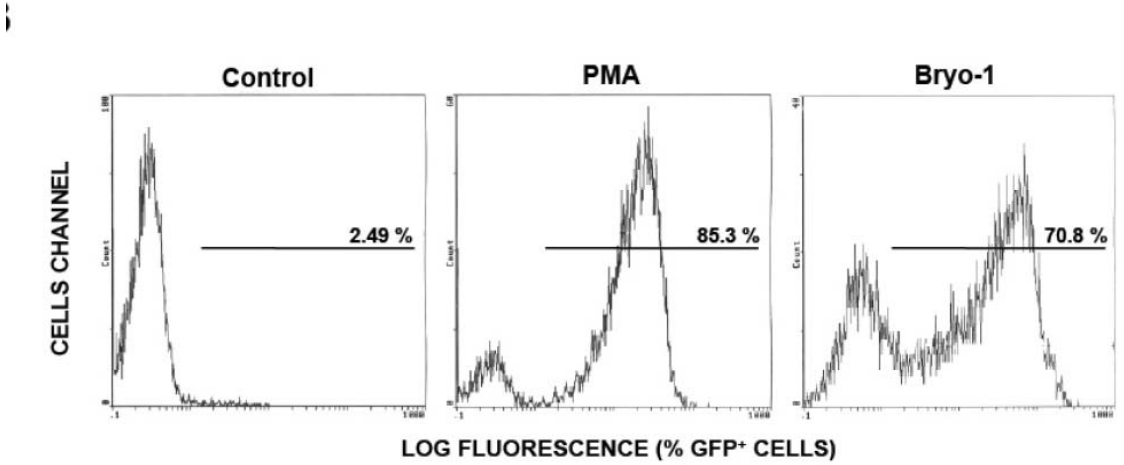
- Non-tumor-promoting phorbol esters



- PKC agonist/antagonist
- Evaluated for cancer therapy (phase I-II)

Bryostatin antagonizes HIV-1 latency





Pérez M. Current HIV Res 2010

Bryostatin-1 and HDAC Inhibitors Synergise to Reactivate HIV-1 Latency

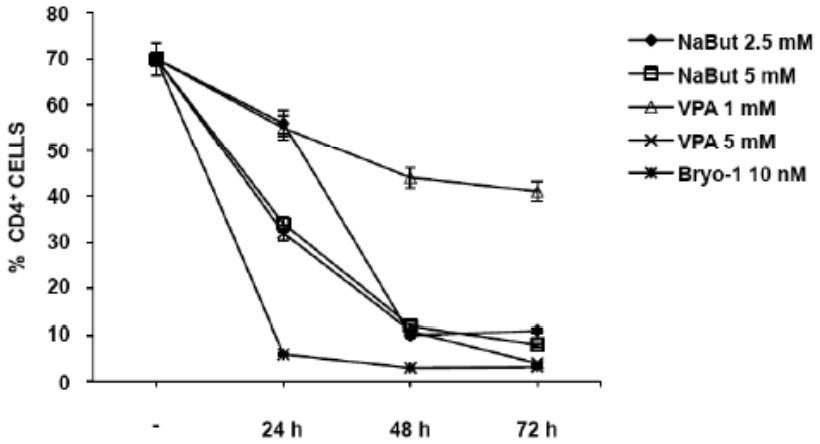
		HDAC Inhibitors								
		-	VPA (mM)			TSA (nM)			NaBut (mM)		
			1	2.5	5	100	200	400	1	2.5	5
Bryo-1 (nM)	-	3.9 ± 0.8	6.3 ± 1.2	8.6 ± 0.1	9.1 ± 0.4	9.7 ± 0.6	16.5 ± 0.8	21.4 ± 1.9	11.2 ± 2.1	16.1 ± 1.8	17.8 ± 1.5
	1	9.0 ± 4.3	16.4 ± 3.2	22 ± 2.8	29.7 ± 1.9	29.6 ± 3.3	45.1 ± 3.0	50.2 ± 2.5	41.0 ± 3.3	47.6 ± 3.0	54.0 ± 1.9
	10	49.2 ± 8.7	63.1 ± 12.9	67.1 ± 0	71.5 ± 9.1	67.4 ± 7.6	74.3 ± 6.0	80.1 ± 5.0	73.1 ± 7.8	77.2 ± 8.7	81.2 ± 9.6

* Values represent the percentage of GFP+ cells (mean ± SD).

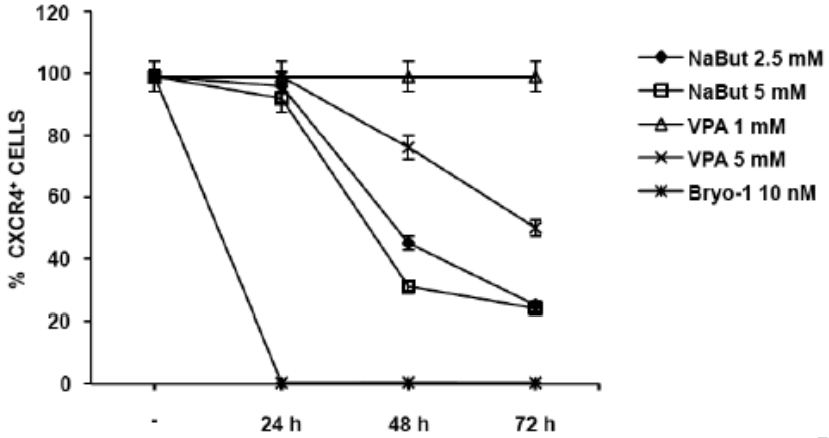
Pérez M. Current HIV Res 2010

Bryostatin-1down-regulates the expression of the HIV-1 receptors CD4 and CXCR4

A



B

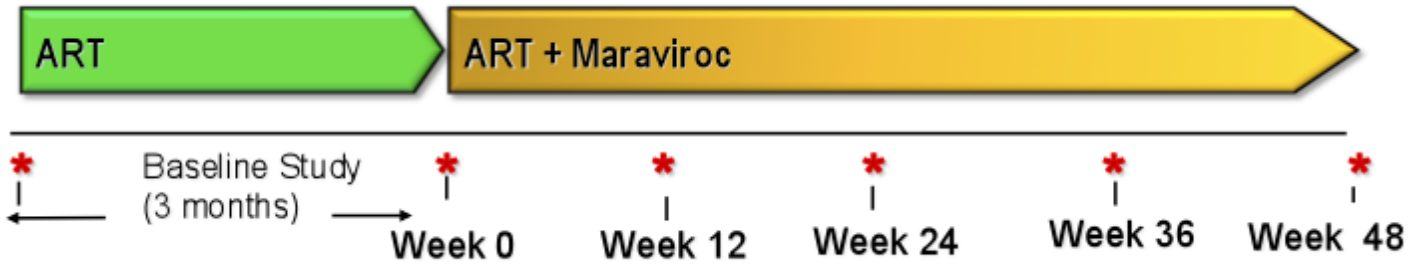


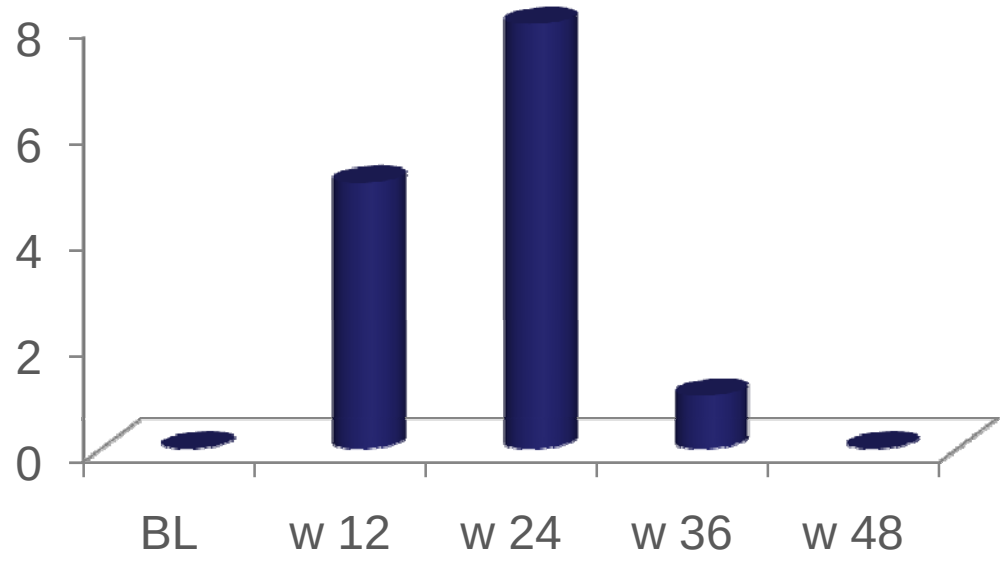
Pérez M. Current HIV Res 2010

Ensayo Clínico BRYOLAT

- Ensayo en fase I, unicéntrico, aleatorizado doble ciego
- Estudio comparativo de dos dosis, con un grupo control
- Dosis única de Briostatina-1
  - Estudio basal (IUPM y otros)
  - Estudios tras administración de briostatina
- Valoración de eficacia y seguridad

Intensification trial with MVC

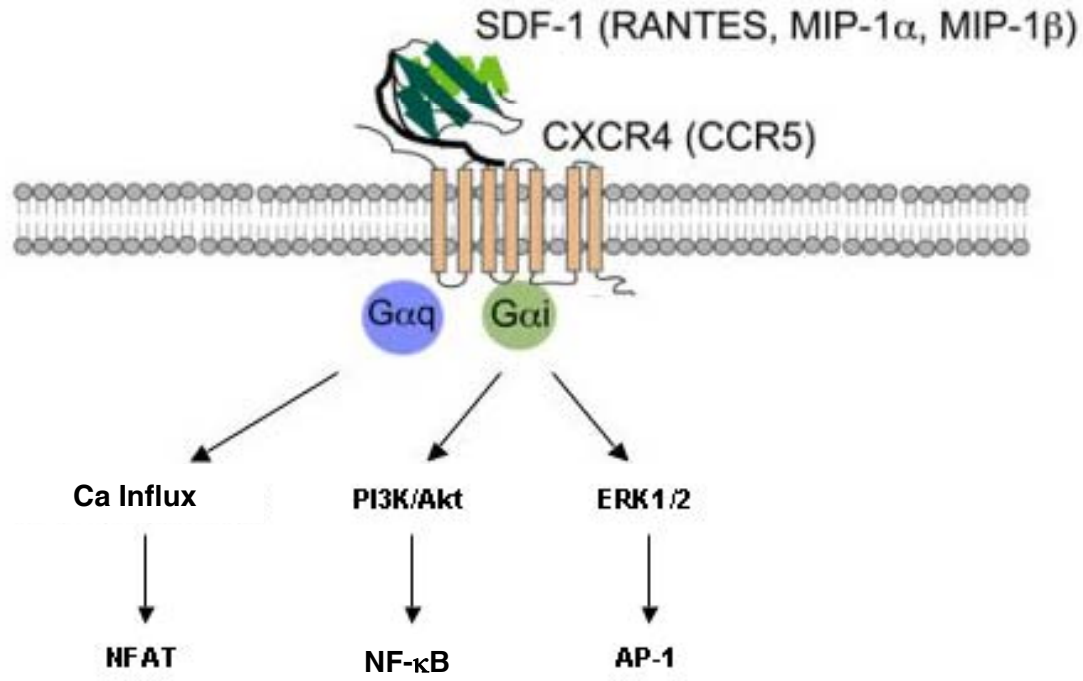




Gutiérrez C et al, PLoS ONE 2011

CCR5 signaling

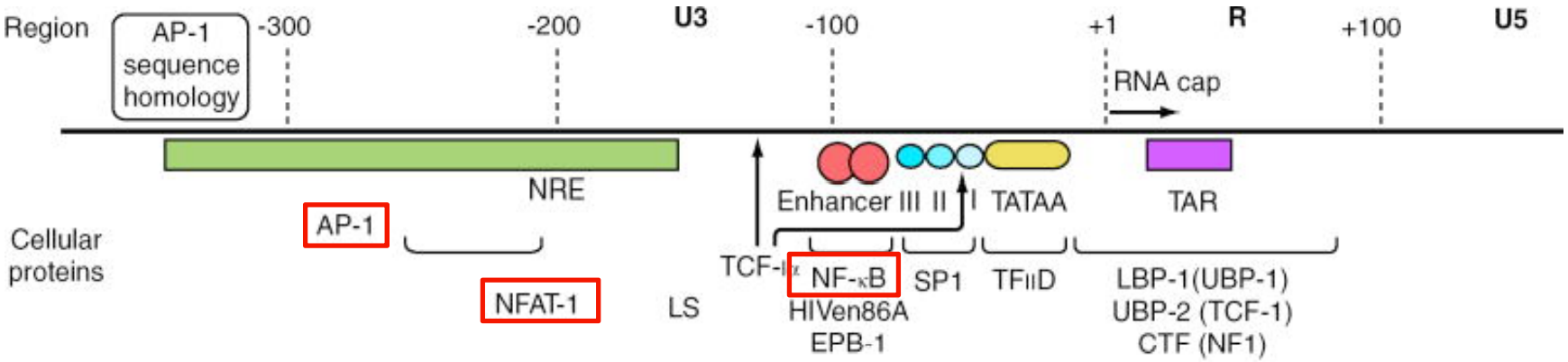
- CCR5 signaling can activate pathways leading to transcription, in a cellular activation status-dependent fashion



Modified from Wu Y et al. PLoS Pathog 2009

HIV-1 LTR structure

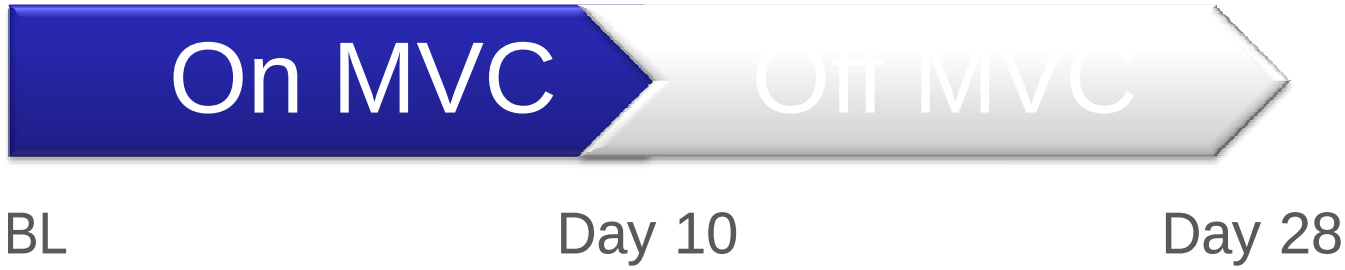
- Cellular factors controlling HIV-1 transcription include NF-κB, NFAT and AP-1



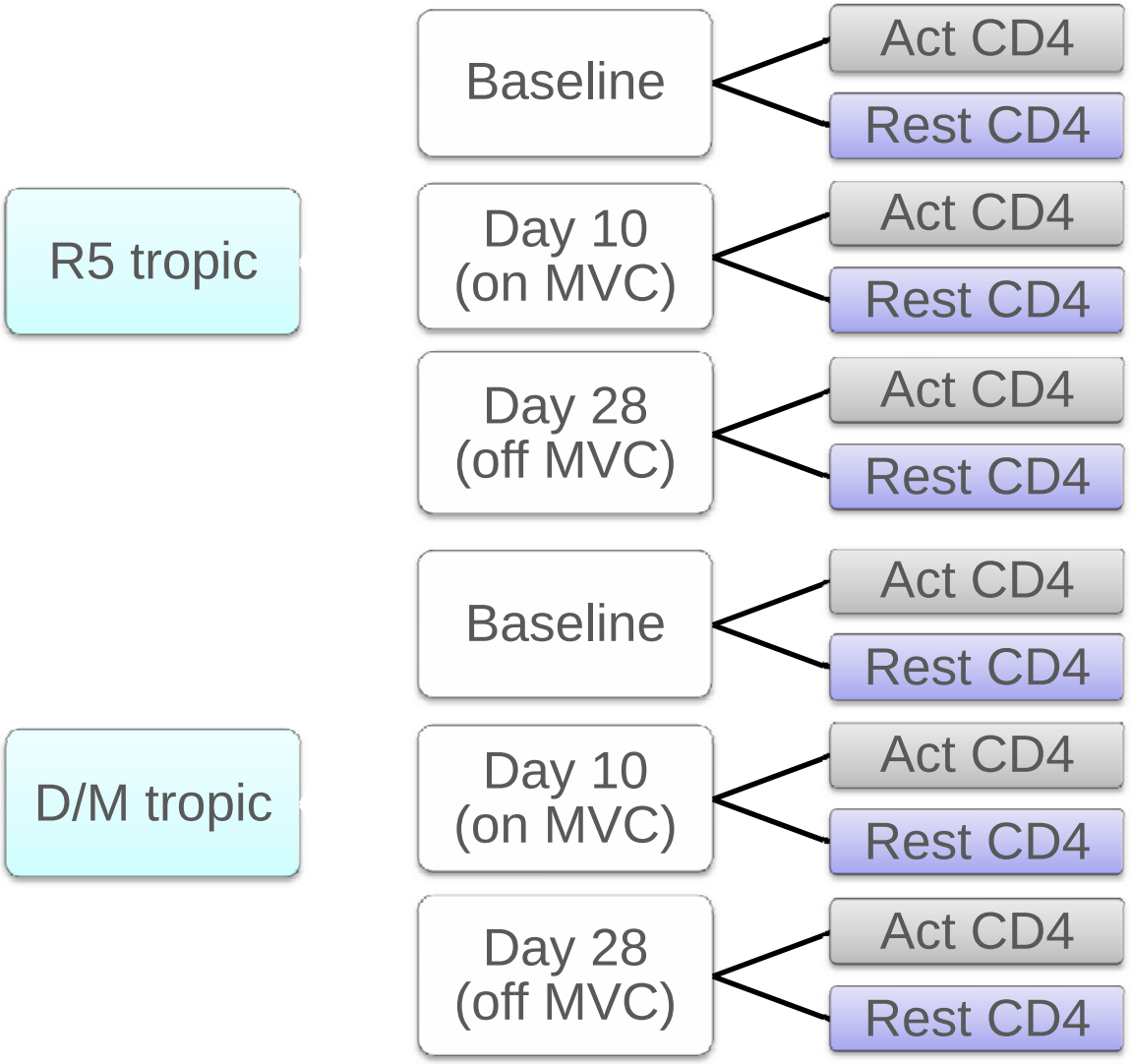
Cleghorn FR et al. Mandell 6th Ed

Subjects and Methods

- TROPISMVC (NCT01060618):
  - naïve HIV-1-infected patients
  - CCR5 and non-CCR5 tropic viruses



Materials and Methods



NF-κB activity in R5 patients

Patient (Tropism)	NF-κB activity (FC)			
	Activated CD4 T cell		Resting CD4 T cell	
	Day 10 (on MRV)	Day 28 (off MRV)	Day 10 (on MRV)	Day 28 (off MRV)
27 (R5)	5.3	0.2	7.6	10.4
28 (R5)	18.0	0.2	4.6	5.3
35 (R5)	0.0	0.6	4.6	1.2
29 (R5)	7.1	3.4	17.6	10.1

- Activity of NF-κB was detected in 4/6 patients with R5 tropic viruses

NF-κB activity in D/M patients

Patient (Tropism)	NF-κB activity (FC)			
	Activated CD4 T cell		Resting CD4 T cell	
	Day 10 (on MRV)	Day 28 (off MRV)	Day 10 (on MRV)	Day 28 (off MRV)
50 (D/M)	4.8	1.8	9.1	10.5
57 (D/M)	1.3	1.9	2.6	10.8

- ...and in 2/3 patients with D/M tropic viruses

NFAT activity

Patient (Tropism)	NFAT activity (OD 450nm)					
	Activated CD4 T cell			Resting CD4 T cell		
	BL	Day 10 (on MRV)	Day 28 (off MRV)	BL	Day 10 (on MRV)	Day 28 (off MRV)
27 (R5)	0.130	0.562	0.247	0.084	0.069	0.072
28 (R5)	0.084	0.126	0.091	0.054	0.077	0.069
35 (R5)	0.110	0.073	0.078	0.076	0.075	0.071
39 (R5)	0.105	0.082	0.076	0.069	0.076	0.090
40 (R5)	0.076	0.088	0.075	0.080	0.073	0.075
50 (D/M)	0.113	0.079	0.079	0.082	0.097	0.113
56 (D/M)	0.289	0.074	0.100	0.125	0.091	0.107
57 (D/M)	0.120	0.084	-	0.077	0.077	-

Nuevos estudios con MVC

- Completar estudios in vitro
  - Confirmar antagonismo de la latencia
  - Confirmar reactivación del VIH latente
  - Determinar la vía (NF-kB, AP-1)
  - Determinar el mecanismo (mediado por CCR5 u otro)

- Si se confirma, ¿ensayo clínico de interrupción de tratamiento?

Prerequisites to achieve a cure

- Complete suppression of viral replication
  - ART intensification?
- Elimination of latently infected cells
  - Anti-latency drugs?
  - Immunotoxins? Gene therapy? Others?
- Prevention of new cell infection
  - Gene therapy?
  - Pharmacological blockade (i.e. CCR5 inhibitors, integrase inhibitors)?

What happened in the Berlin patient?

- **Prerequisite 1:**
  - The HIV-1 reservoir was significantly reduced by the depletion of the T cell pool by the conditioning regimen for stem cell transplantation
- **Prerequisite 2:**
  - HIV-1 replication was abrogated in the remaining T cell fraction due to the absence of activated CD4 T cells under immunosuppressive treatment
- **Prerequisite 3:**
  - No new cell infection occurred since repopulating CD4 T cells were resistant to CCR5-tropic HIV-1 infection because of the absence of CCR5 surface expression.

Hutter G, *et al*. *N Engl J Med* 2009;**360**:692-8

Ensayo clínico CHEMOMAR

- Pacientes diagnosticados de linfoma que van a recibir quimioterapia citorreductora
- Se administra maraviroc mientras dura la quimioterapia
- Evaluación del reservorio antes y despues de recibir QT + Maraviroc