

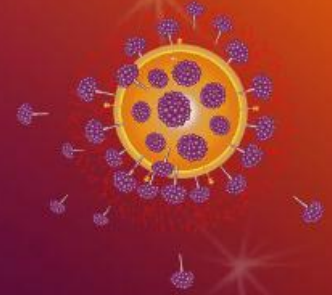
EL DESAFIO DE LA CURACIÓN DEL SIDA

*Pepe Alcami
Unidad de Inmunopatología del SIDA
Red Española de Investigación en SIDA
Instituto de Salud Carlos III. Madrid*



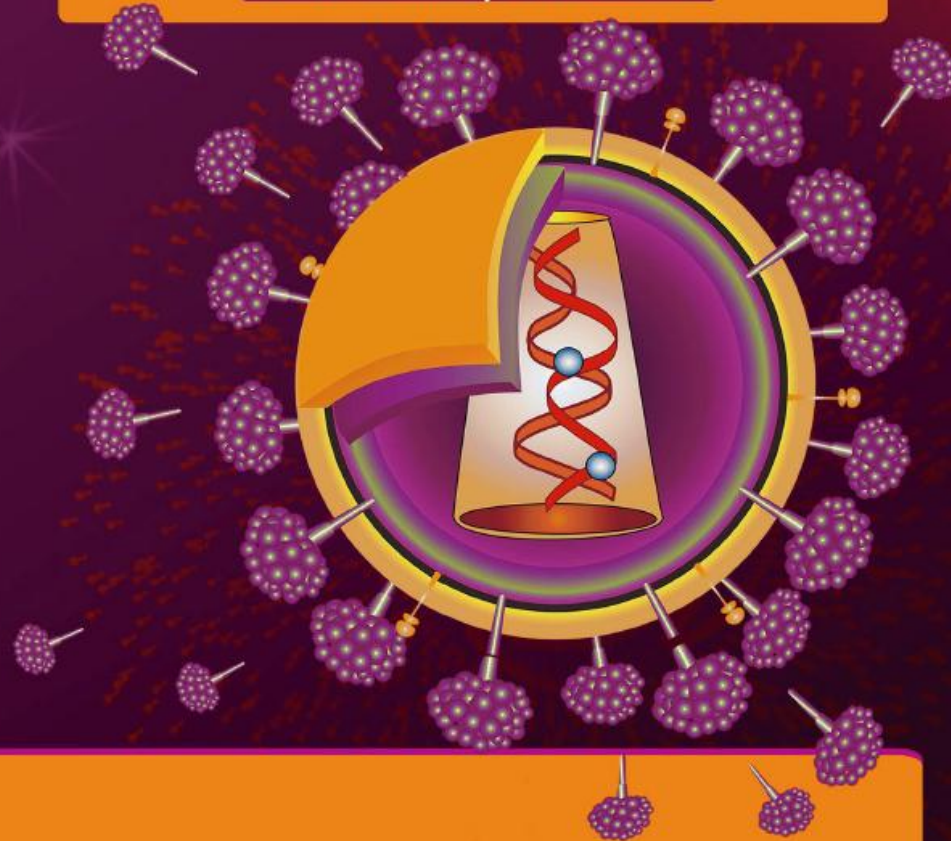
RETIC-RIS |

Son Espases
hospital universitari



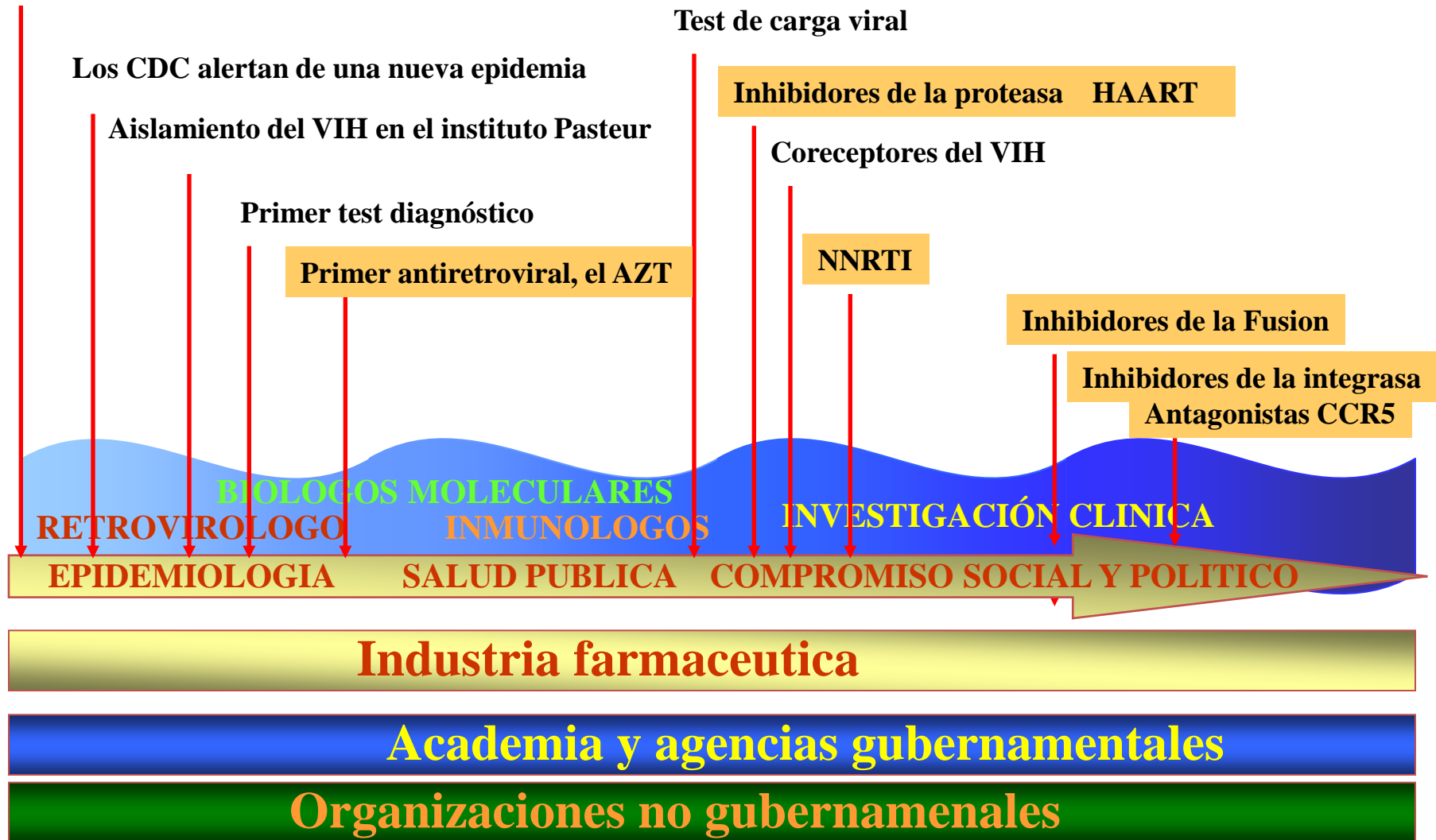
**XI CURSO EN ANTIBIOTERAPIA
ACTUALIZACIÓN EN INFECCIÓN POR VIH**

30 - 31 de marzo y 1 de abril 2017



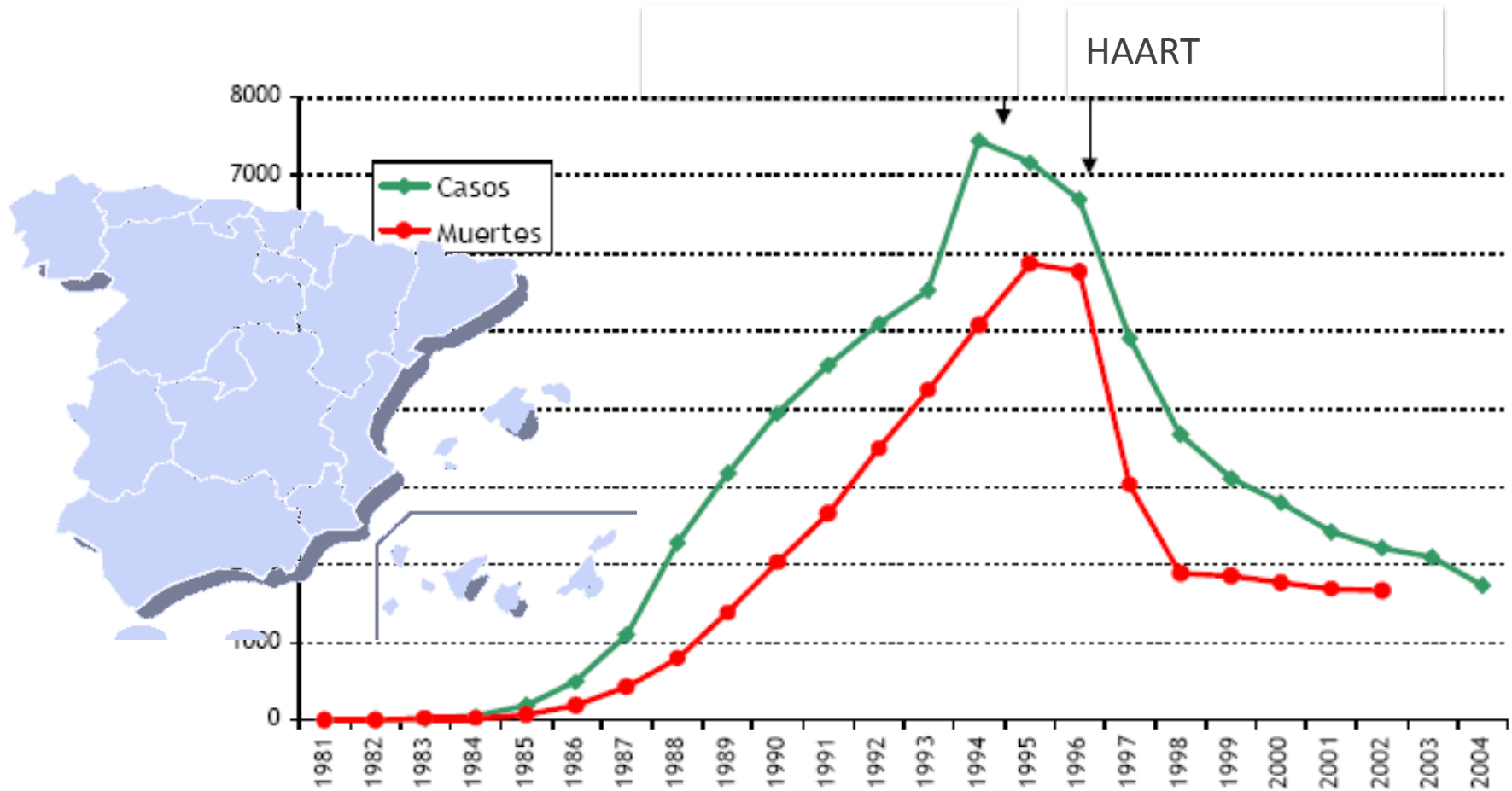
35 AÑOS DE HISTORIA. EL SKI LINE DEL SIDA

Descripcion de los primeros casos de SIDA



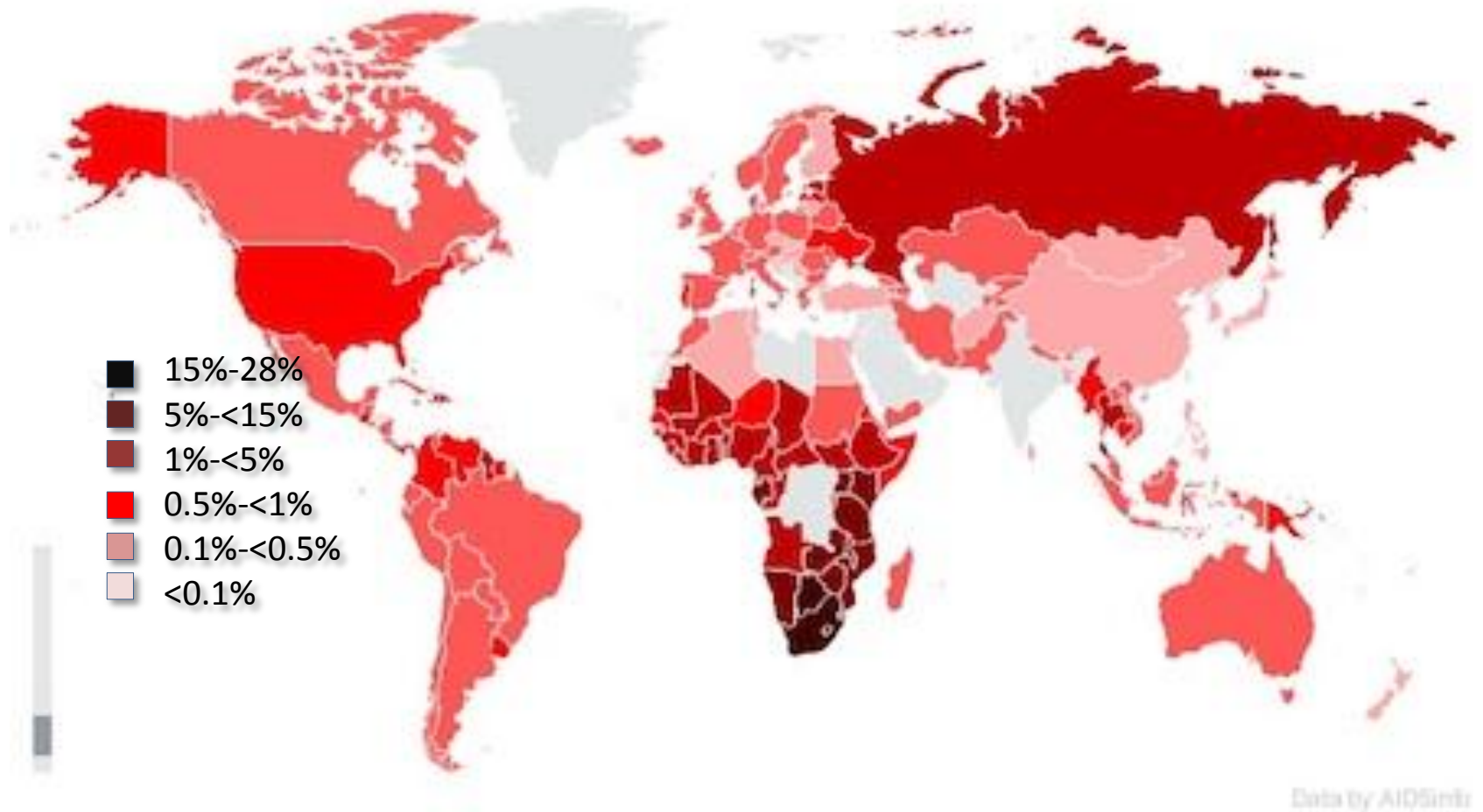
30 AÑOS DE VIH/SIDA

HISTORIA DE EXITO → TRATAMIENTO



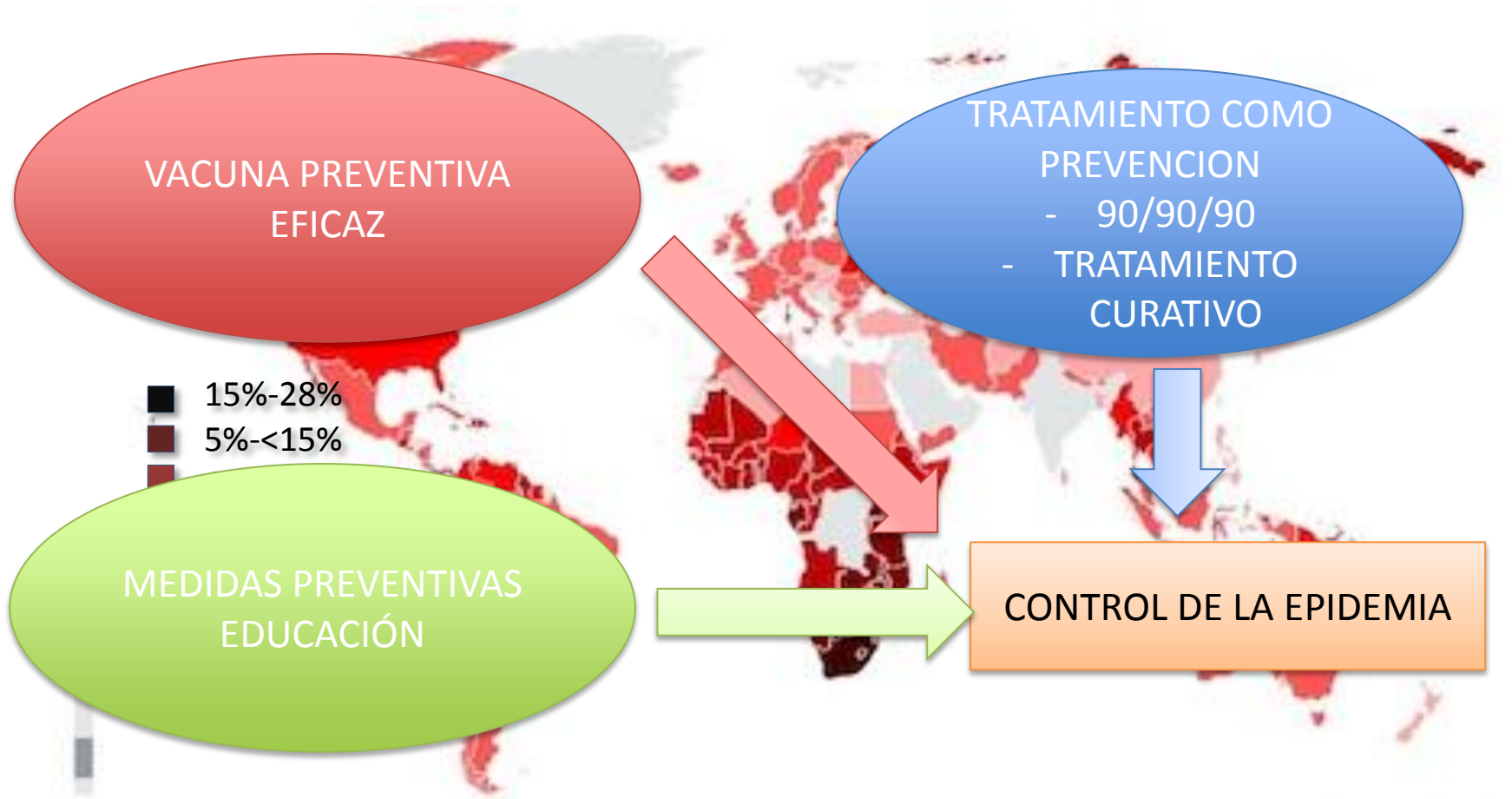
35 AÑOS DE VIH/SIDA

HISTORIA DE FRACASOS → LA EPIDEMIA NO HA SIDO CONTROLADA



ESTRATEGIAS DE CONTROL-CURACIÓN

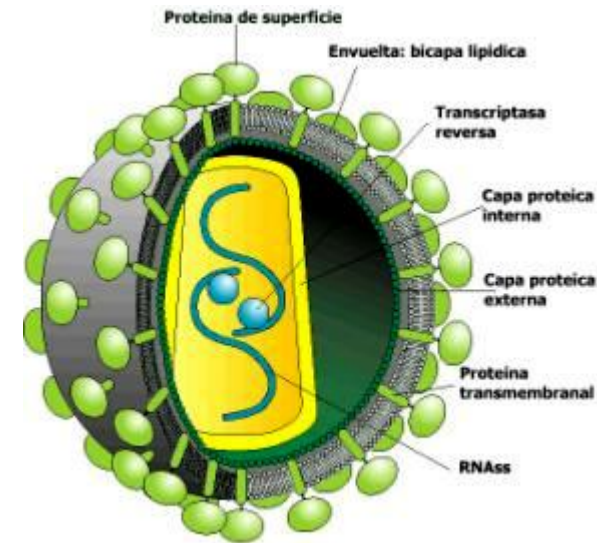
- Nivel individual
- Nivel general



ERADICACION O CURA FUNCIONAL DEL VIH “LA PROXIMA FRONTERA”

DESAFIOS PARA ALCANZAR LA CURA DE LA INFECCIÓN POR VIH

- **Mecanismos moleculares**
 - Latencia y persistencia viral
- **Reservorios virales**
 - Celulares y anatómicos
 - Dinámica de los reservorios
 - Medición de los reservorios
- **Estrategias para la curación**



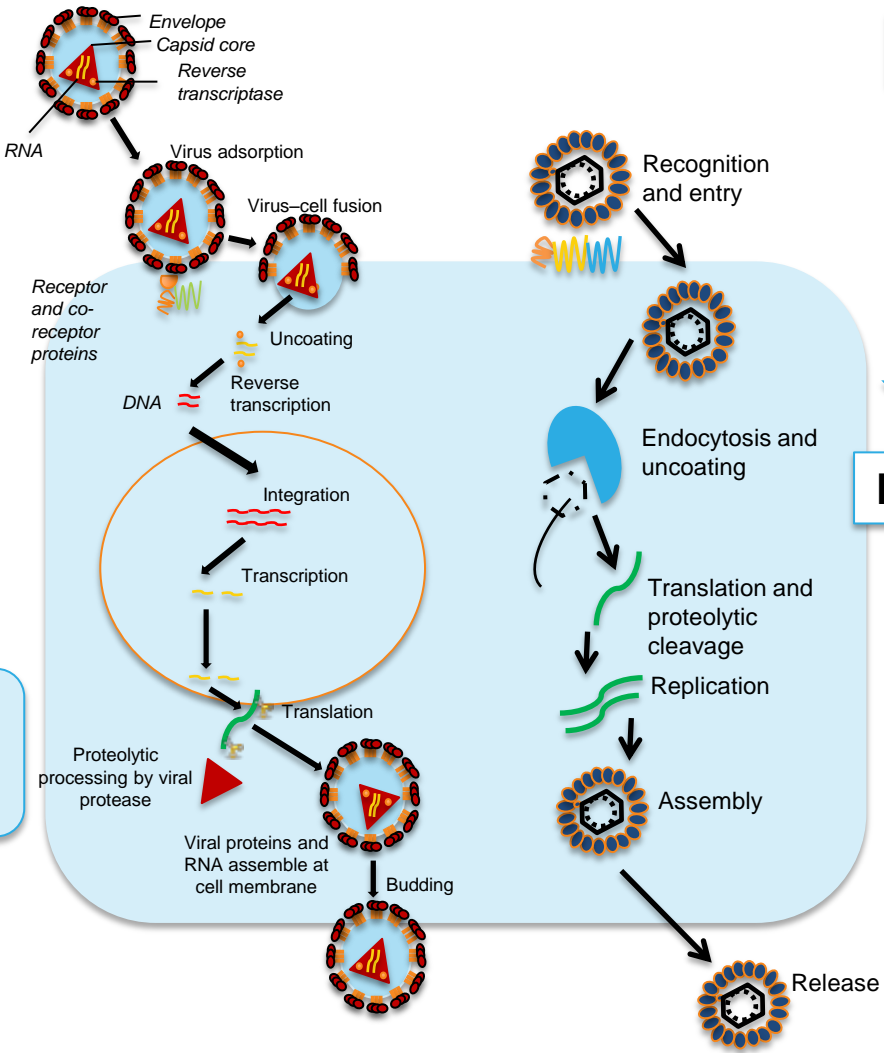
Dos estrategias de persistencia viral

Persistencia del genoma en la célula infectada



**Herpes virus
Papilloma virus
Hepatitis B virus
Retrovirus**

TRATAMIENTO ANTIVIRAL EFICAZ = NO CURATIVO



Replicación mantenida



Efecto citopático



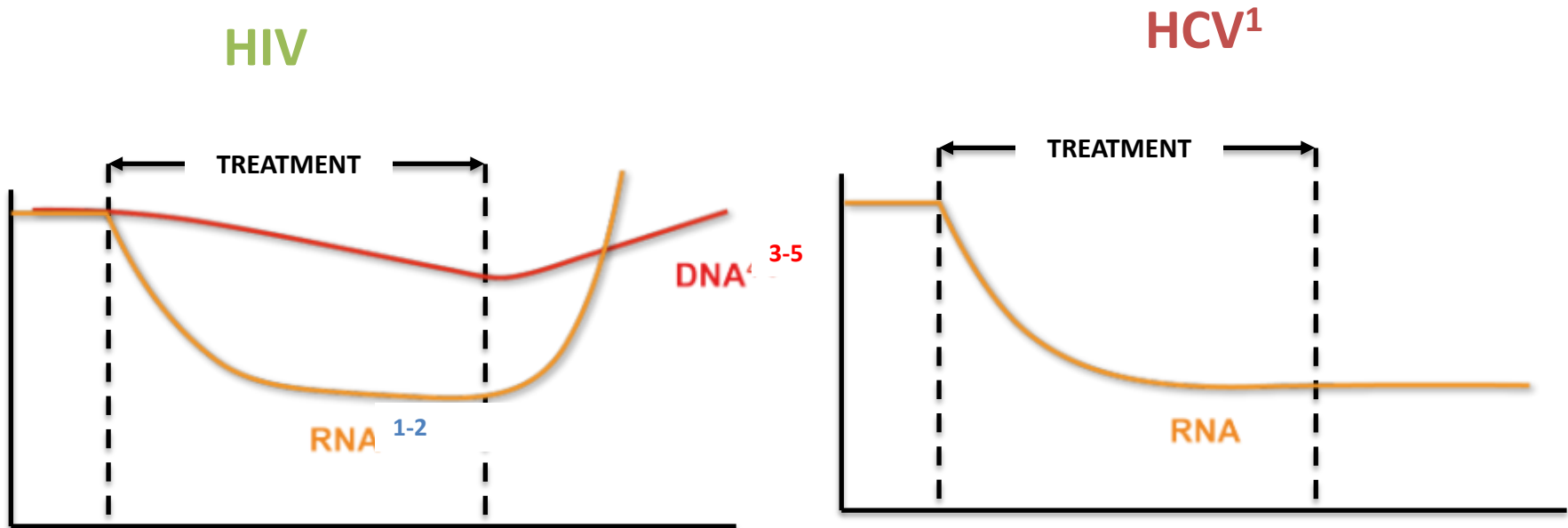
Infección de nuevas dianas

TRATAMIENTO ANTIVIRAL EFICAZ = CURACION

1. De Clercq E. *Nat Rev Drug Discov* 2002;1(1):13-25. 2. Schaefer E, Chung R. *Gastroenterology* 2012;142(6):1340-50. 3. Boldogh I. Chapter 46: in Baron. *Medical Microbiology* 4th Edition, 1996.

Barreras para la curación

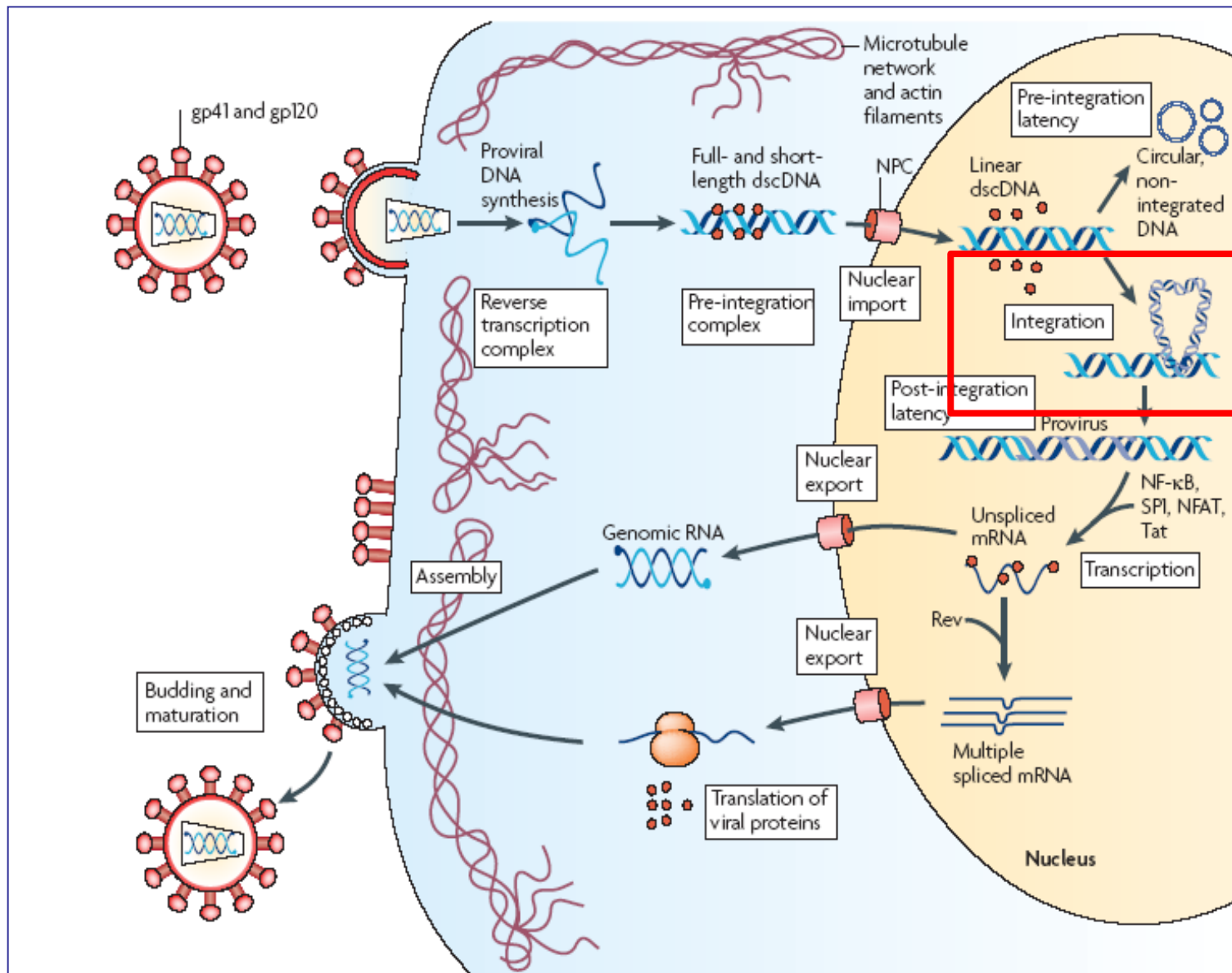
El tratamiento antiviral sólo elimina el virus que replica –ARN-, no los reservorios de ADN



- Existo del tratamiento frente a VHC pero no VIH
- La suspensión del tratamiento origina el repunte viral en >95% de los casos

1. Durand et al. Trends Immunol. 2012;33:554-62. 2. Garcia et al. AIDS 1999;13:F79-86. 3. Ibañez A et al. AIDS 1999;13:1045-1049. 4. Watanabe D et al. BMC Inf Dis 2011;11:146. 5. Van Lint C, Retrovirology. 2013;26;10:67.

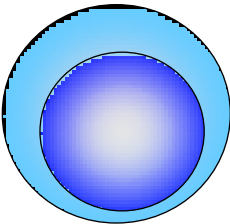
Barreras para la curación. El ciclo del VIH



EL PARADIGMA DE LA LATENCIA Y LA REACTIVACIÓN

Liinfocito CD4 en reposo

Restricción a la infección y la replicación



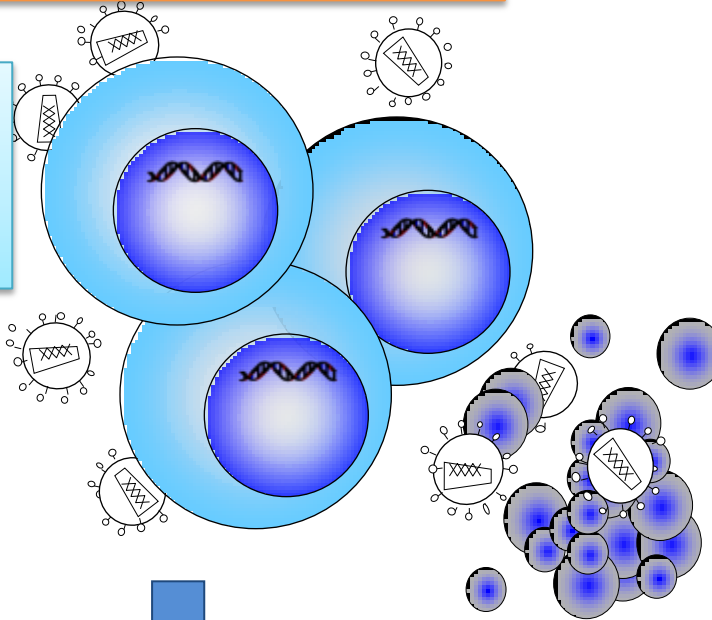
Baja expresión de CCR5 → Entrada
Bajos niveles de dNTPs → Retrotranscripción
Bajos niveles de ATP → Importe nuclear
Ausencia de factores de transcripción

LOS LINFOCITOS CD4 EN REPOSO SON EL GRAN RESERVORIO DEL VIH

Activación LT →

Linfocito CD4 activado

Alta susceptibilidad a la infección y la replicación



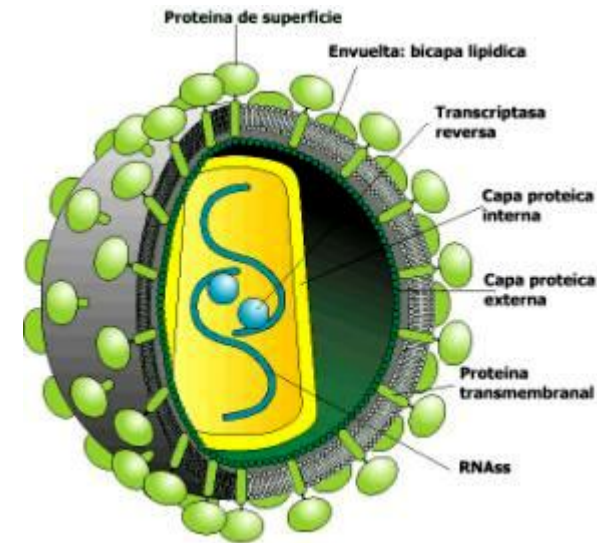
Replicación viral activa

ERADICACION O CURA FUNCIONAL DEL VIH “LA PROXIMA FRONTERA”

DESAFIOS PARA ALCANZAR LA CURA DE LA INFECCIÓN POR VIH

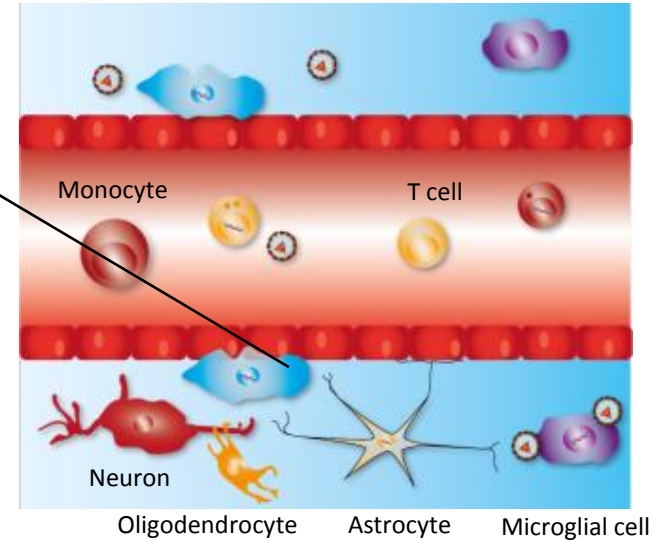
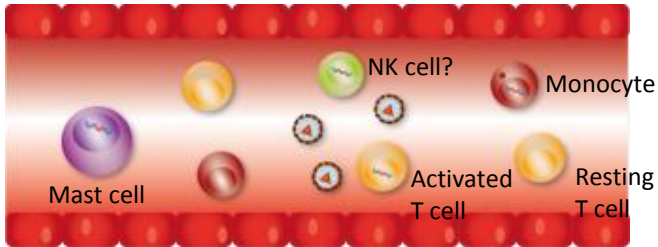
● Reservorios virales

- Celulares y anatómicos
- Dinámica de los reservorios
- Medición de los reservorios

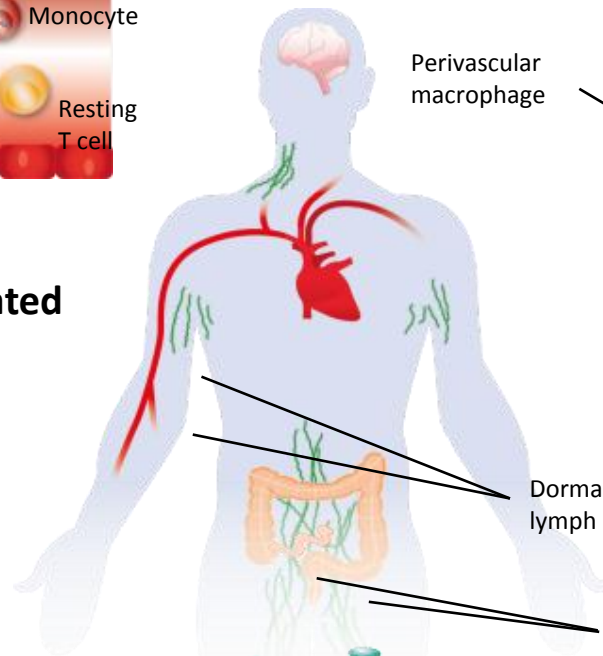
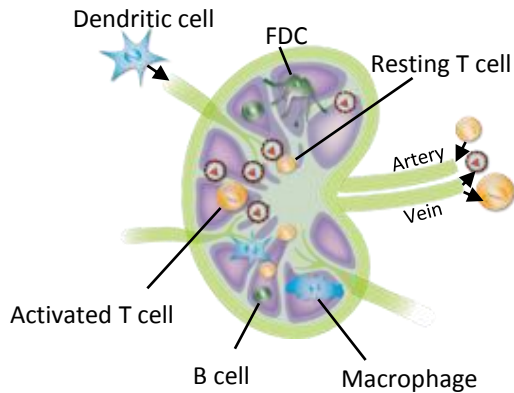


Reservorios anatómicos

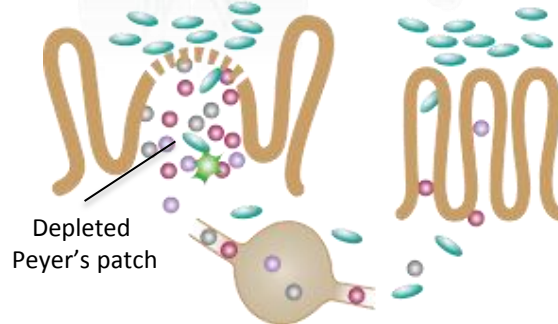
Blood¹



Lymph nodes and gut-associated lymphoid tissue (GALT)^{1,2}



Dormant memory T cells in lymph nodes and blood³



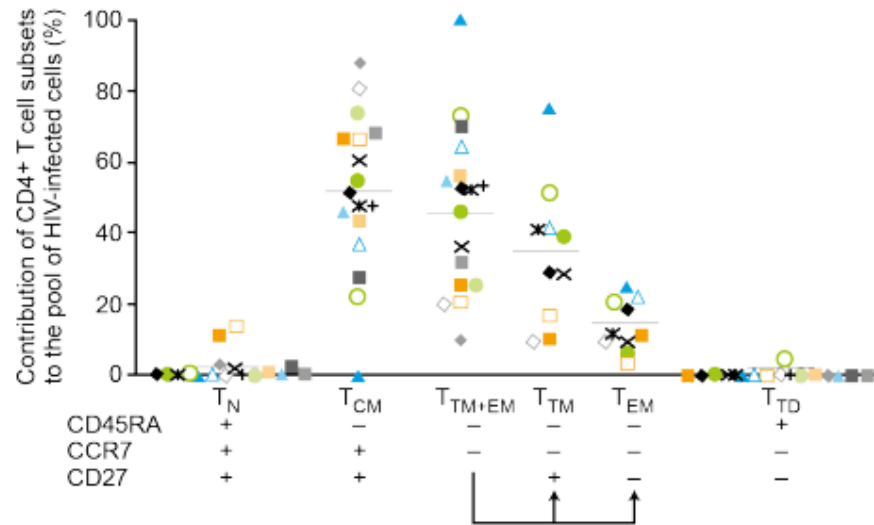
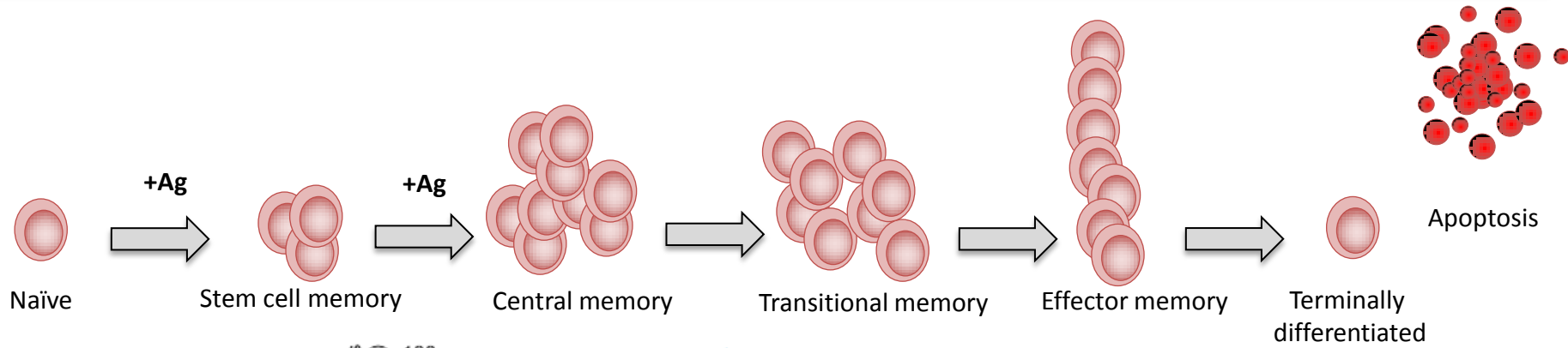
Depleted Peyer's patch

Macrophages and dendritic cells in various tissues (especially in lymph nodes, gut and central nervous system)³

1. Alexaki A, et al. *Curr HIV Res* 2008;6(5):388–400.
2. Yukl SA, et al. *J Infect Dis* 2010;202(10):1553–61.
3. Deeks SG, et al. *Nat Rev Immunol* 2012;12(8):607–14.

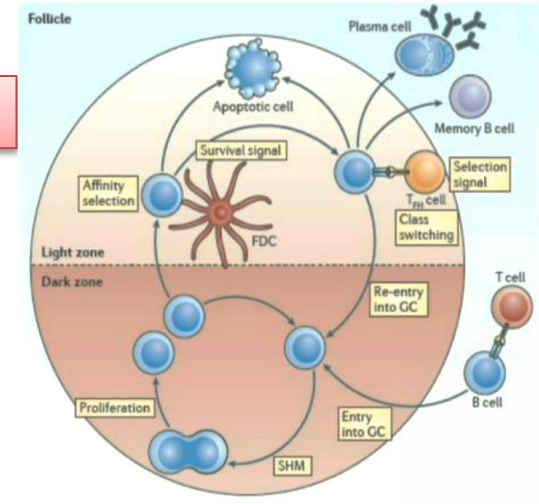
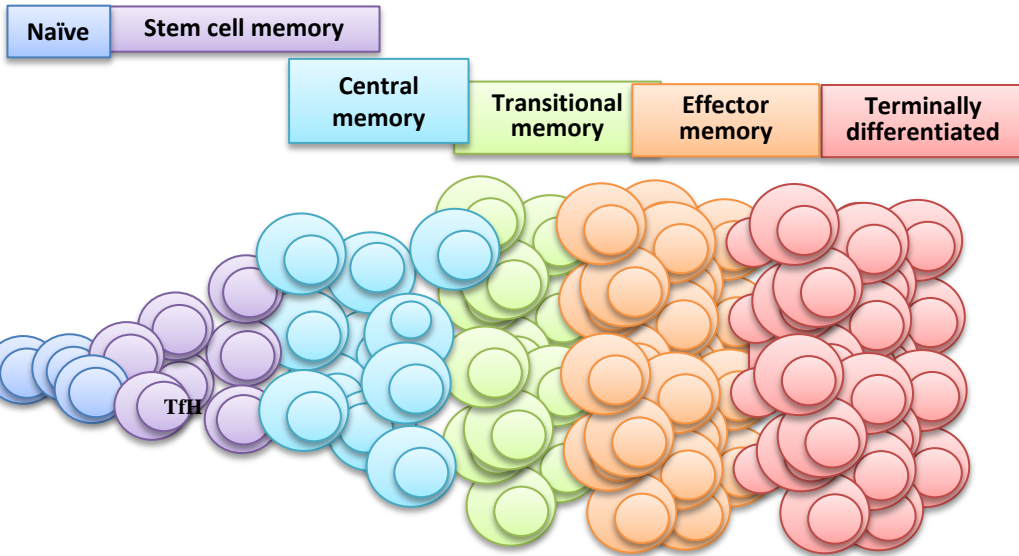
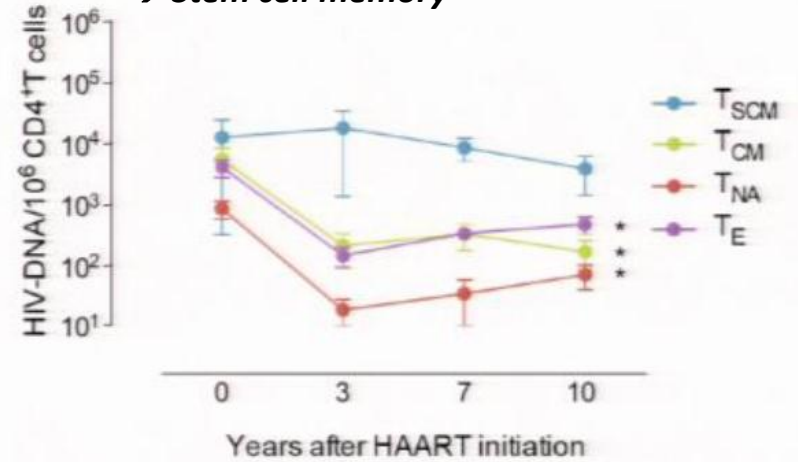
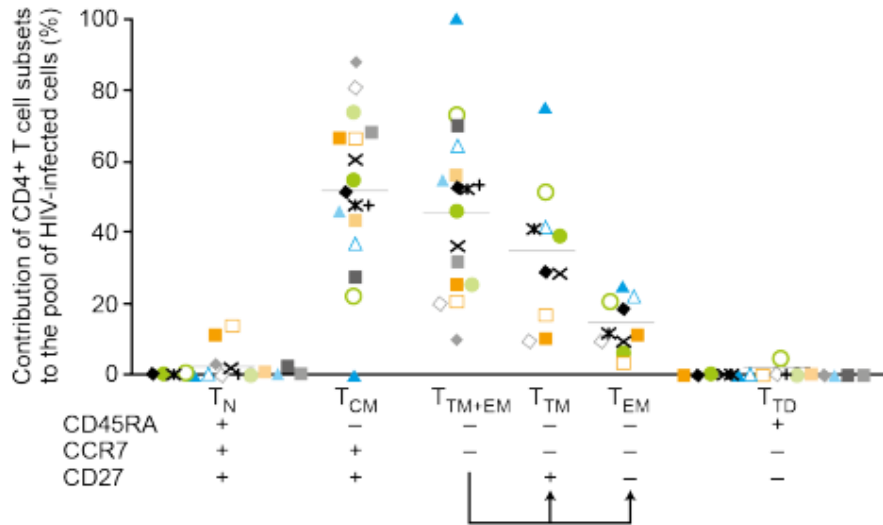
Barriers to HIV cure: Cellular reservoirs? Where is the virus hidden?

Preferential infection of memory CD4 subsets

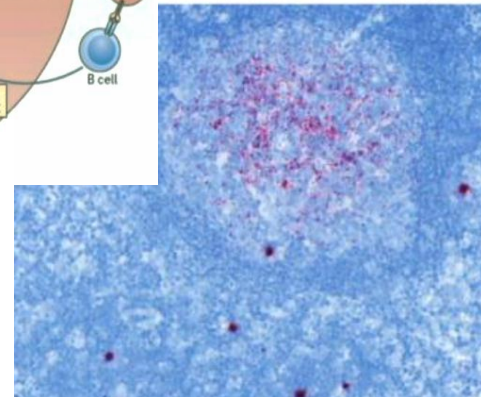


Reservorios celulares: células memoria y TFH

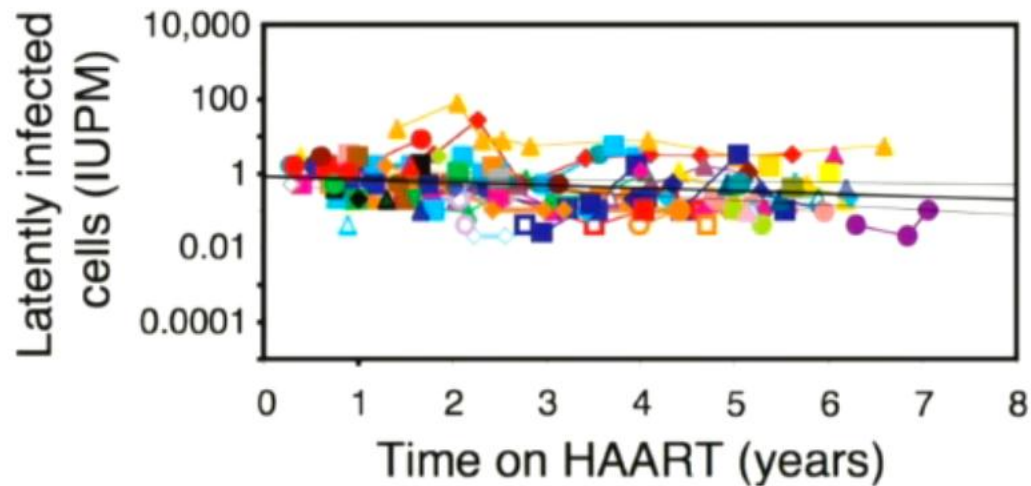
*A new and persistent reservoir
→ Stem cell memory*



LN - 4 wpi



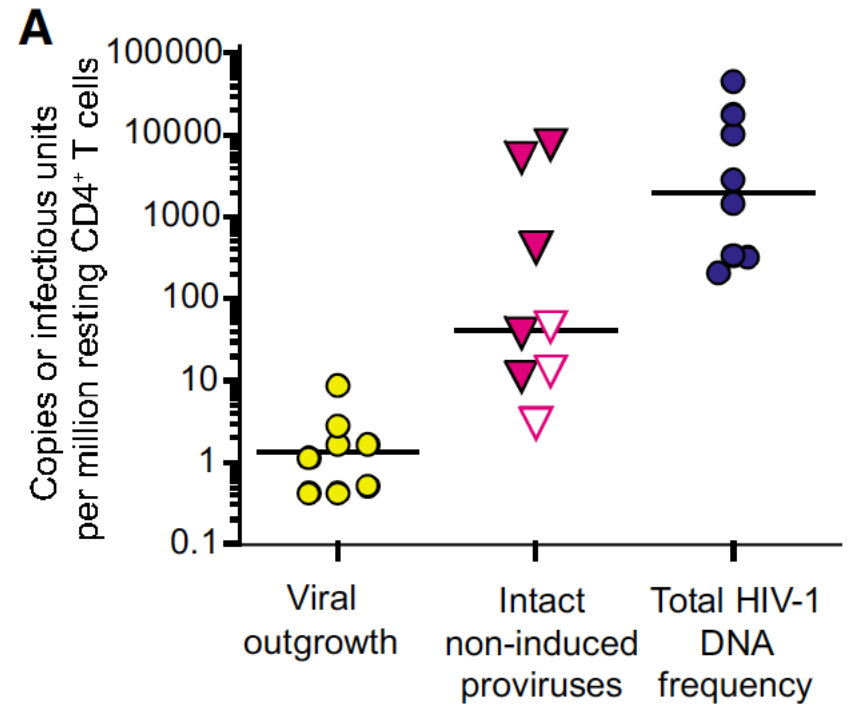
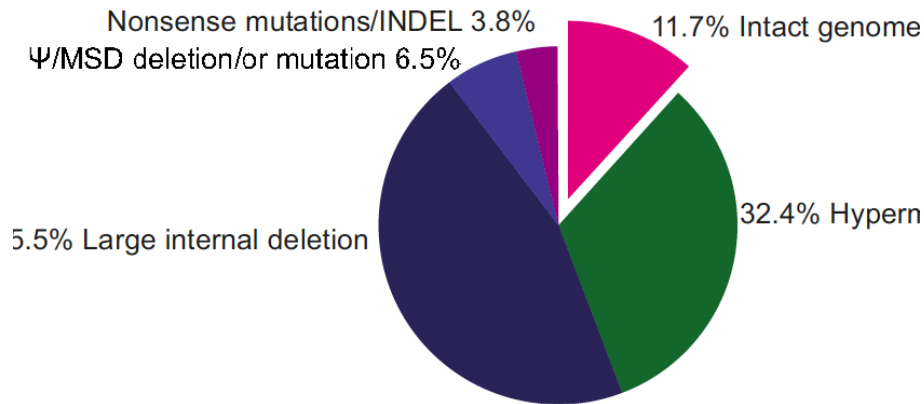
Half life of the latent reservoir



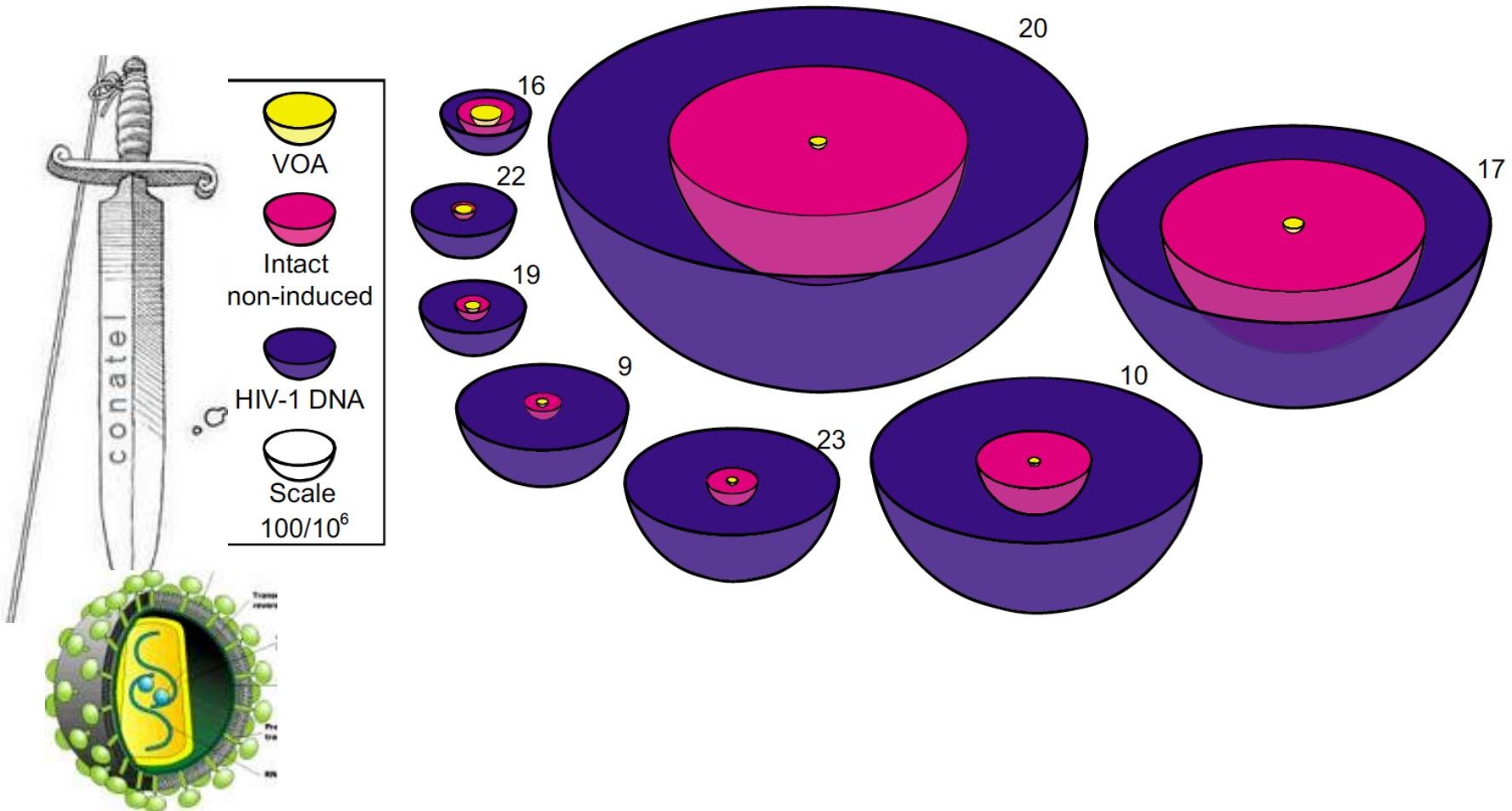
➤ Time on ART to eliminate 10^6 cells: 73.4 years

Reservorios funcionales: defectivos y competentes para la replicación

Replication-competent virus accounts for ~12% of reservoirs

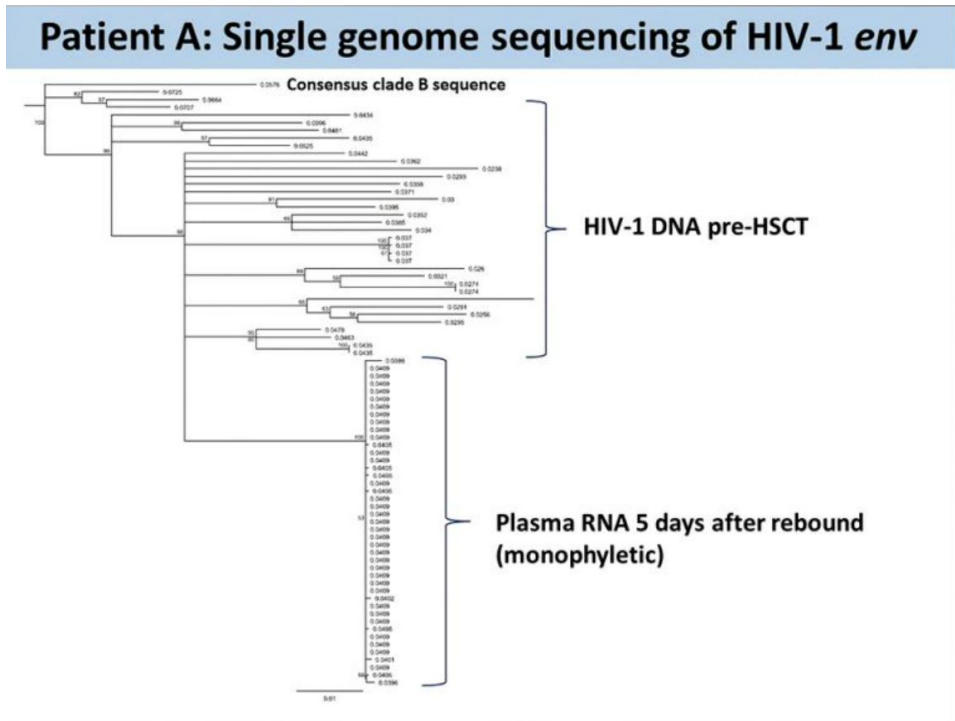
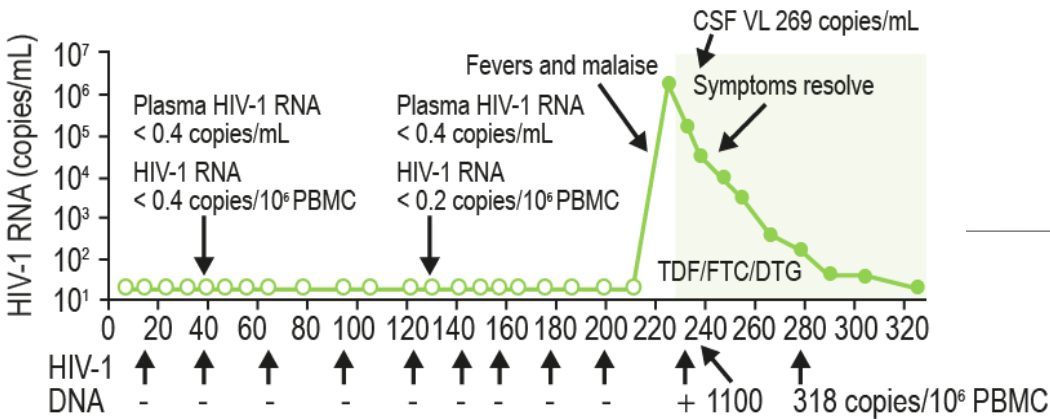
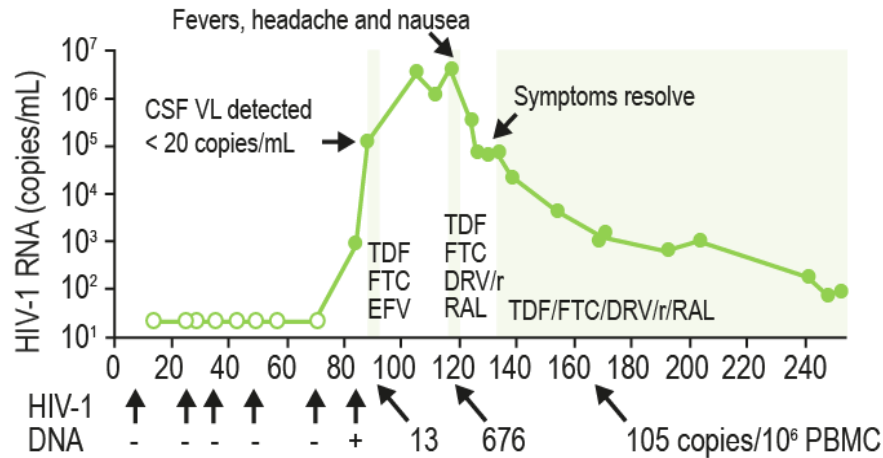


Reservorios funcionales: defectivos y competentes para la replicación

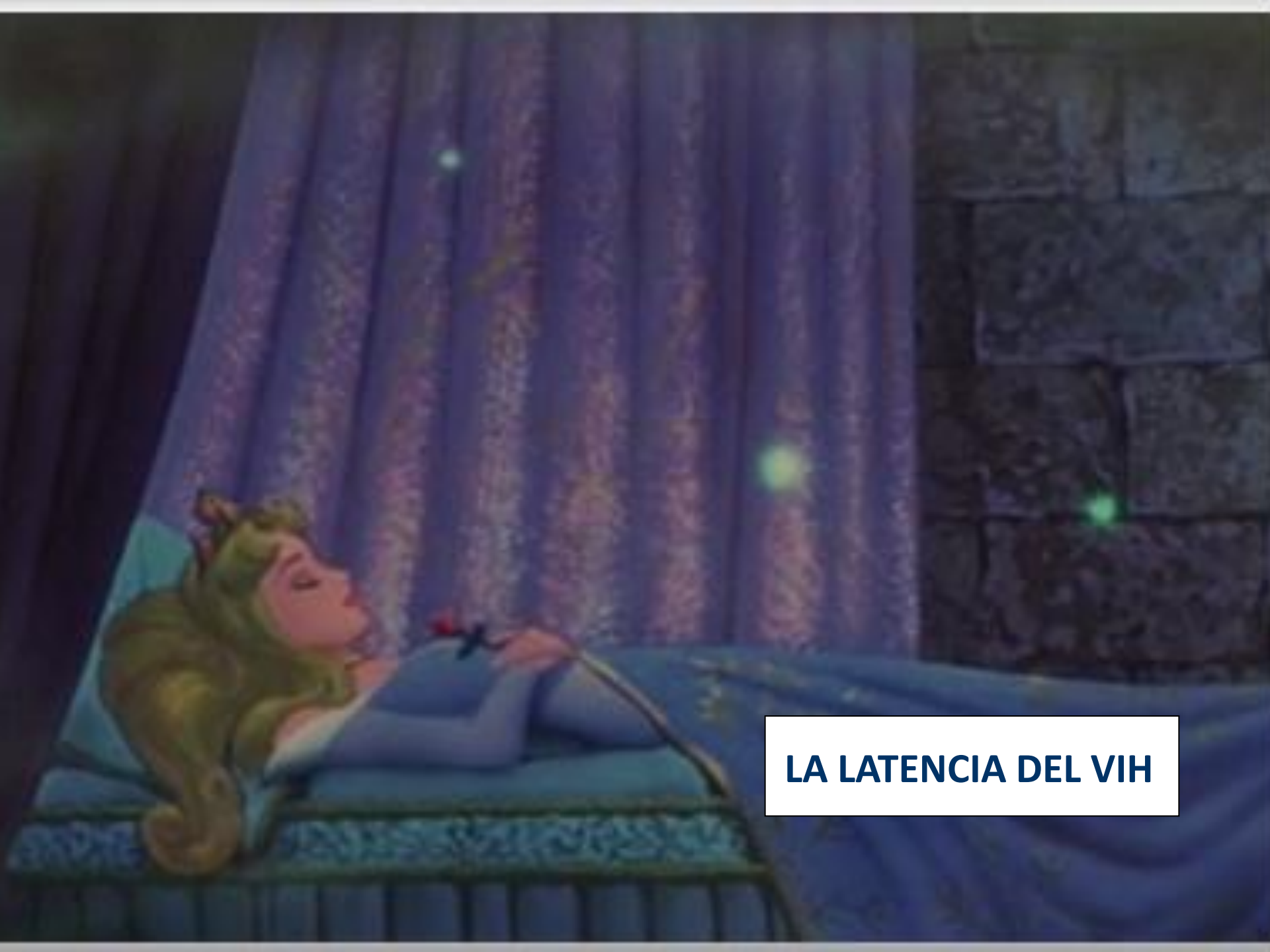


1. Shan L, et al. *Immunity* 2012; 36:491–501. 2. Eisele E & Siliciano RF. *Immunity* 37:377–88. 3. Eriksson S et al. *Plos Pathogens* 2013;9(2);e1003174. 4. Ho et al. *CROI* 2013, abstract #43. 5. Ho et al., *Cell* 2013, in press.

Disappointing news: HIV 'rebound' in the Mississippi baby and Boston patients



1. YuKL SA, et al. PLoS Pathog 2013;9:e1003347. 2. Volberding P. Ann Intern Med 2014;160:505–6. 3. NIAID press release. Available from: <http://www.niaid.nih.gov/news/newsreleases/2014/pages/mississippibabyhiv.aspx> (Accessed June 2015). 4. Henrich TJ, et al. Ann Intern Med 2014;161:319–27.

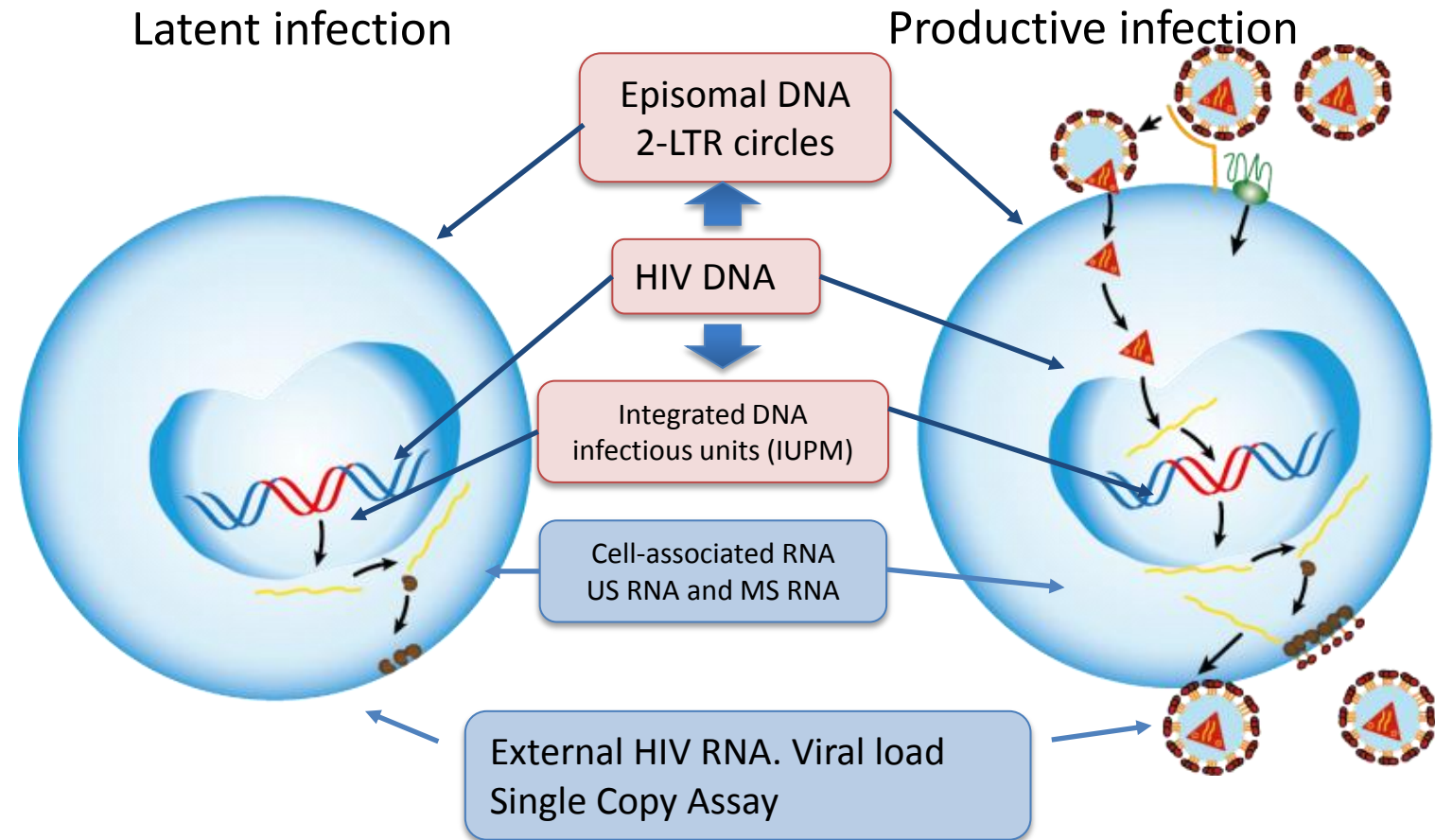


LA LATENCIA DEL VIH

o... la latencia del VIH



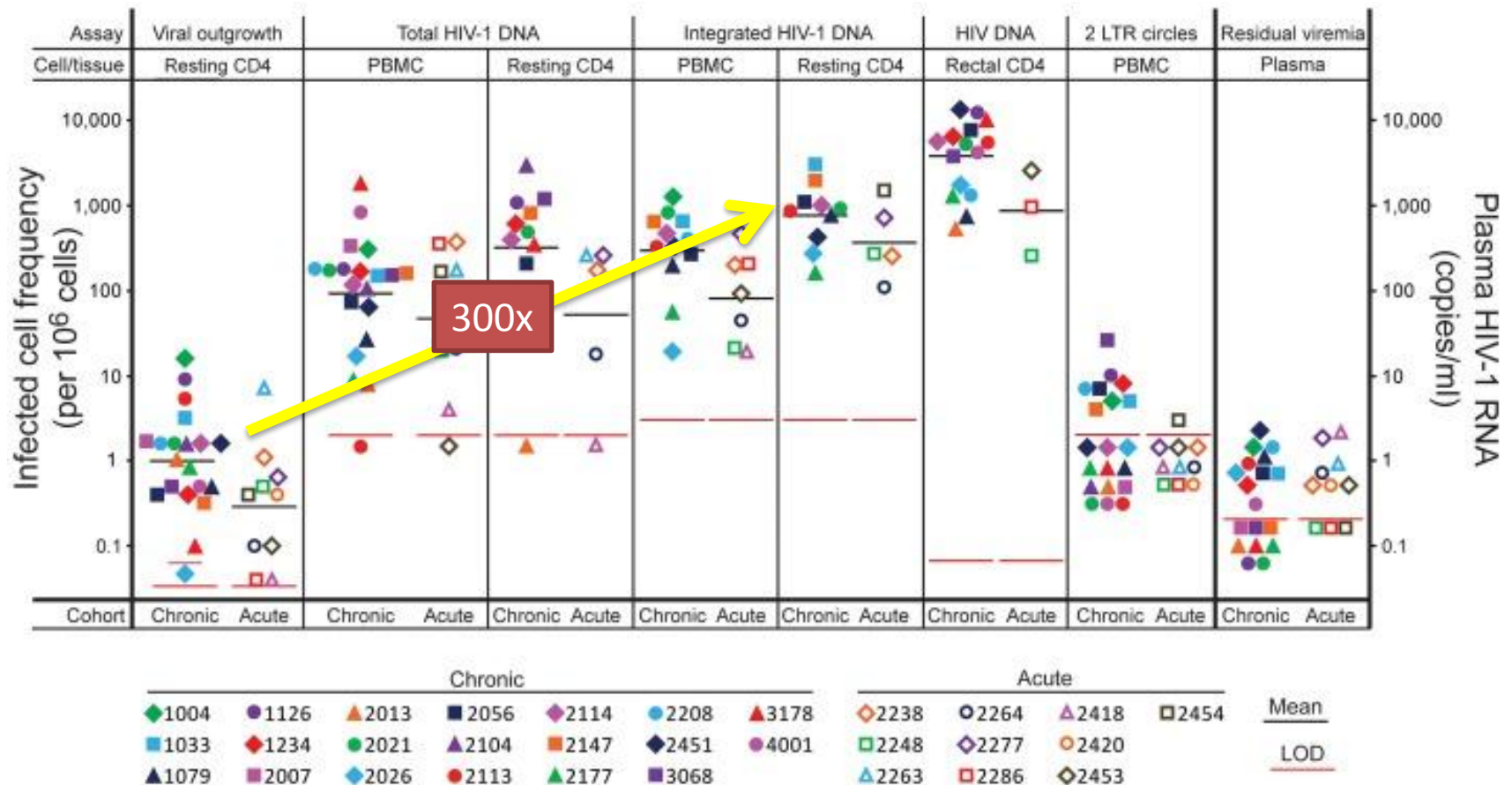
Problema práctico de primer orden ¿cómo medir el reservorio?



But which methods are best in clinical practice?

¿Cómo medir el reservorio “in vivo”?

Different techniques to measure the HIV reservoir
 300 times difference between viral DNA and cultured virus



¿Cómo monitorizar la curación?

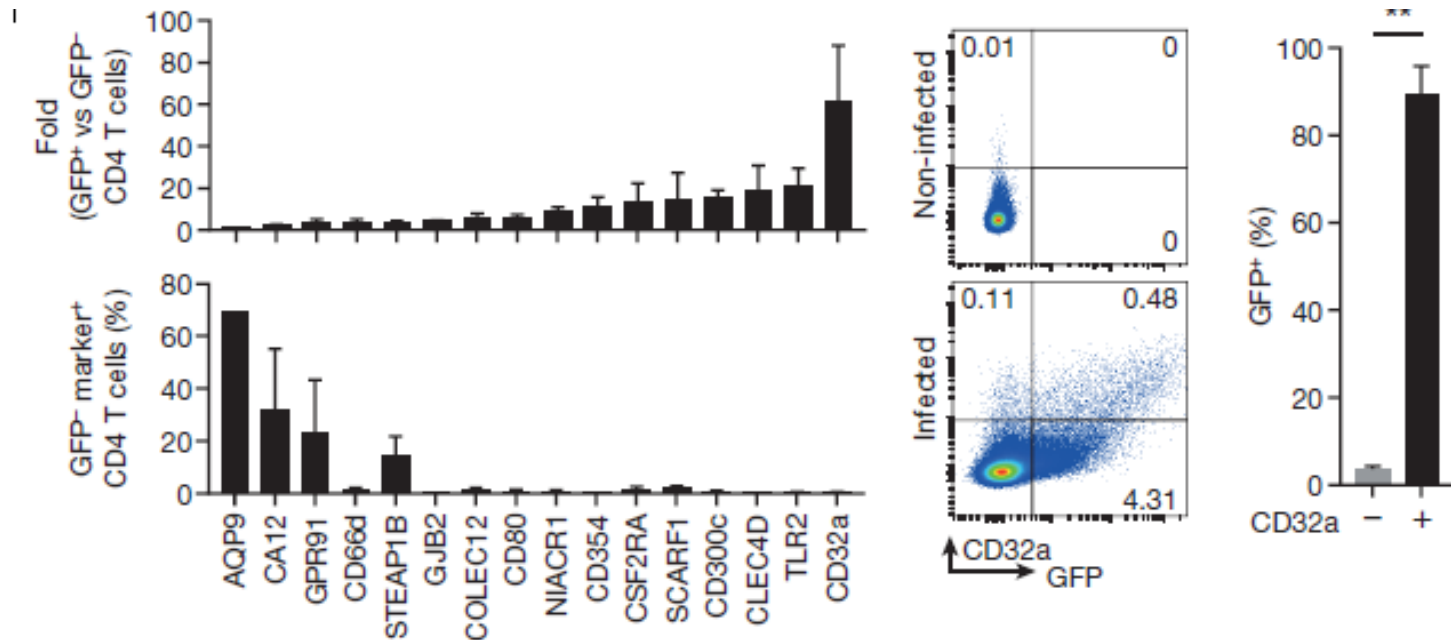
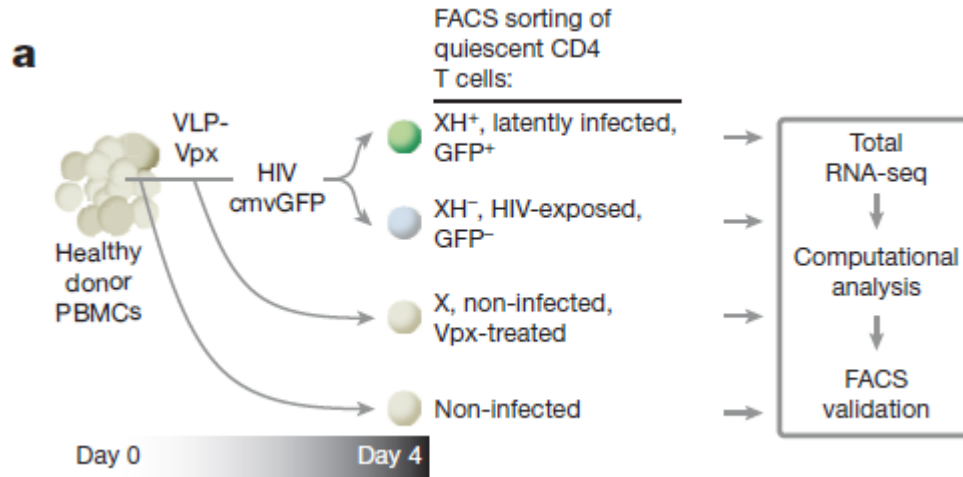
1. No detectar ADN proviral y no estar curado
2. Detectar el ADN proviral y estar curado



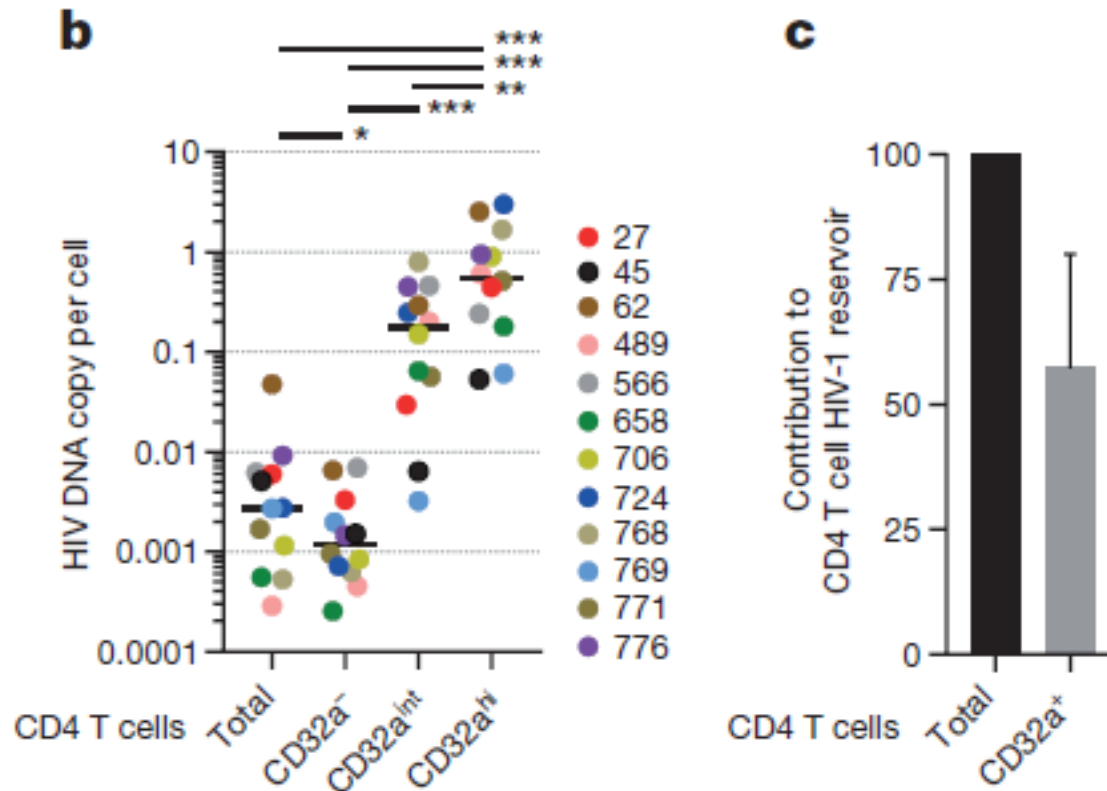
INTERRUPCION DE TRATAMIENTO

- ¿A quien?
- ¿Cuándo?
- ¿Con qué criterios?

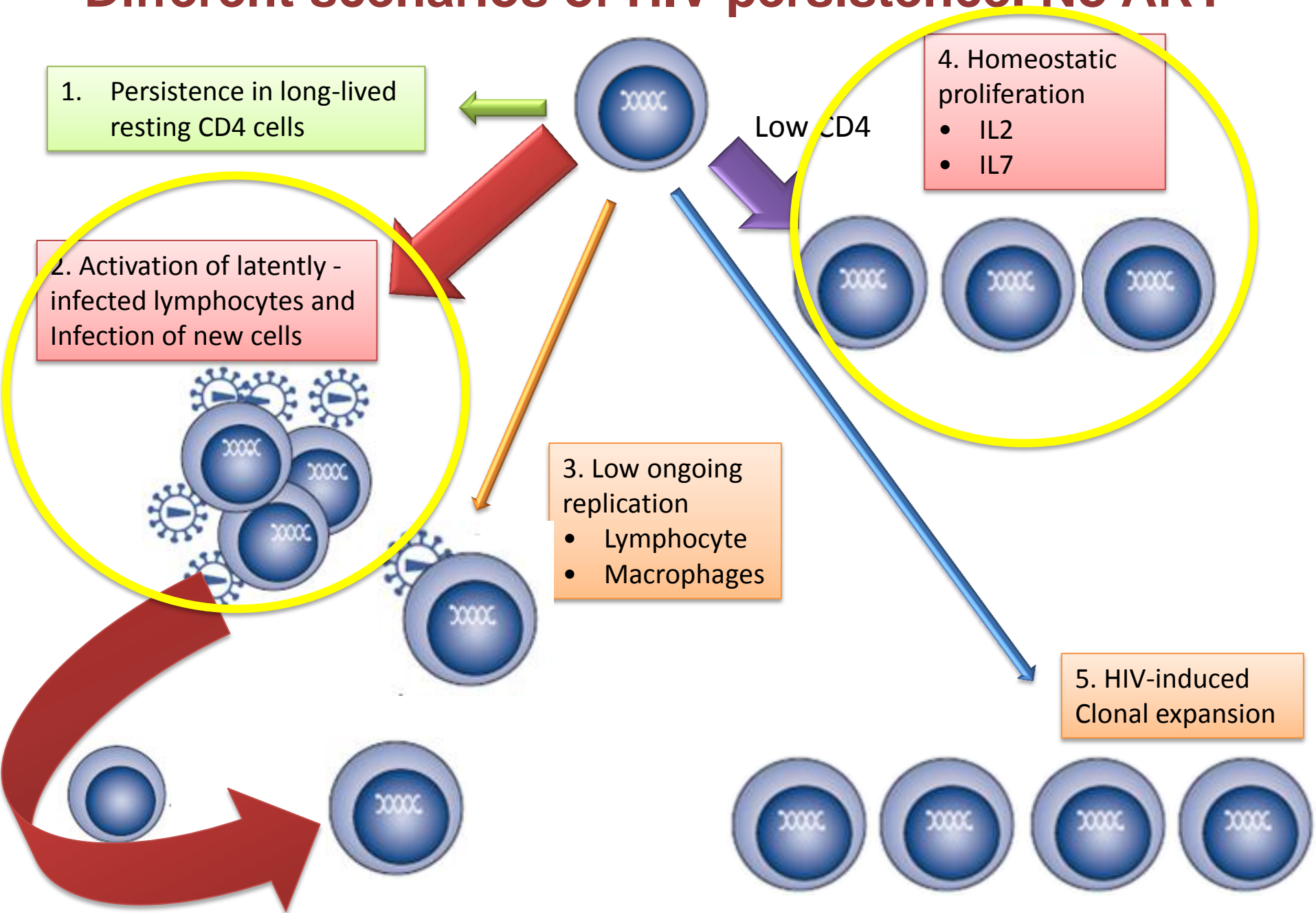
¿Cómo medir el reservorio “in vivo”? *Ultimas noticias*



¿Cómo medir el reservorio “in vivo”? *Ultimas noticias*



Different scenarios of HIV persistence. No ART



Different scenarios of HIV persistence. ART

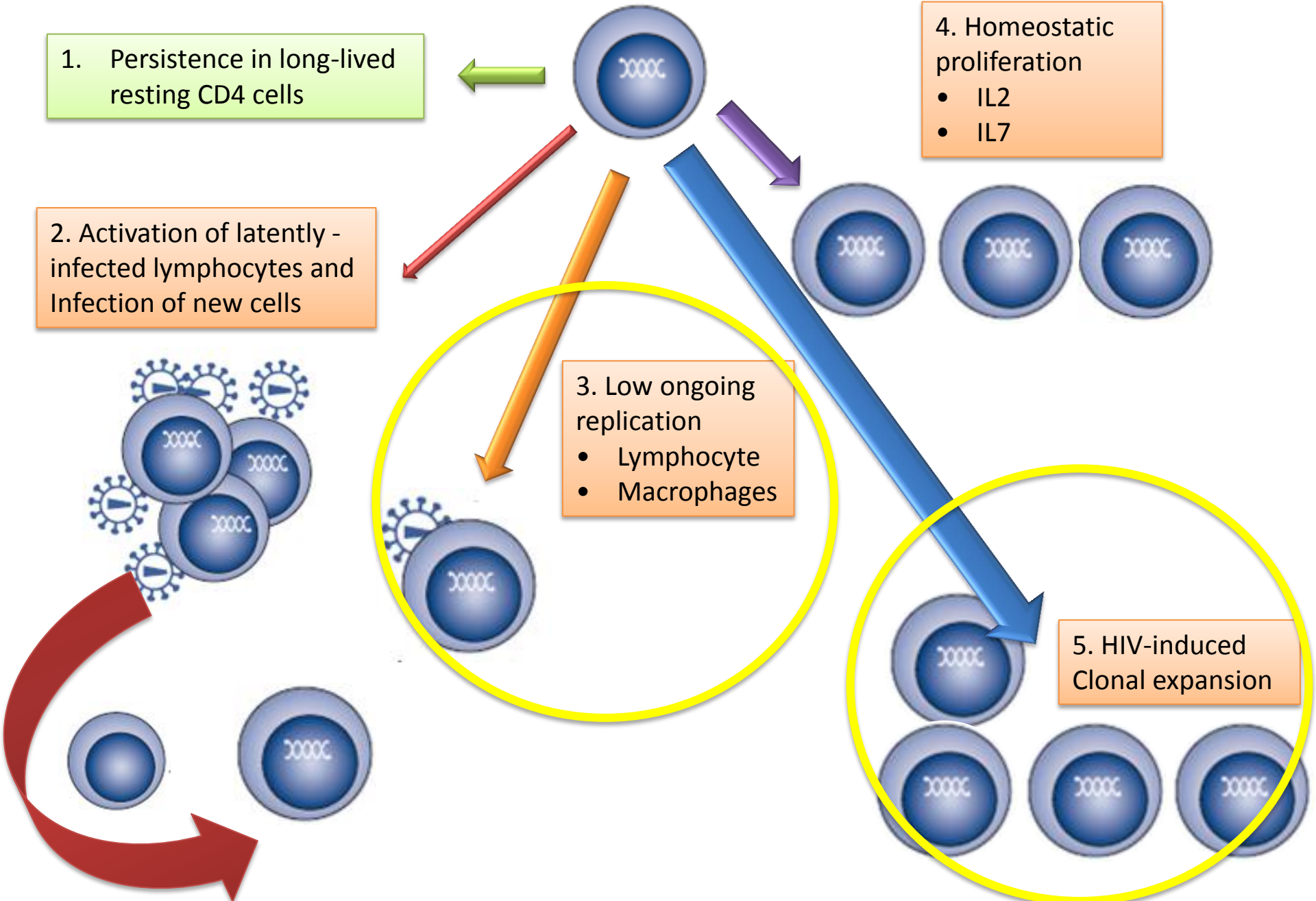
1. Persistence in long-lived resting CD4 cells

2. Activation of latently - infected lymphocytes and Infection of new cells

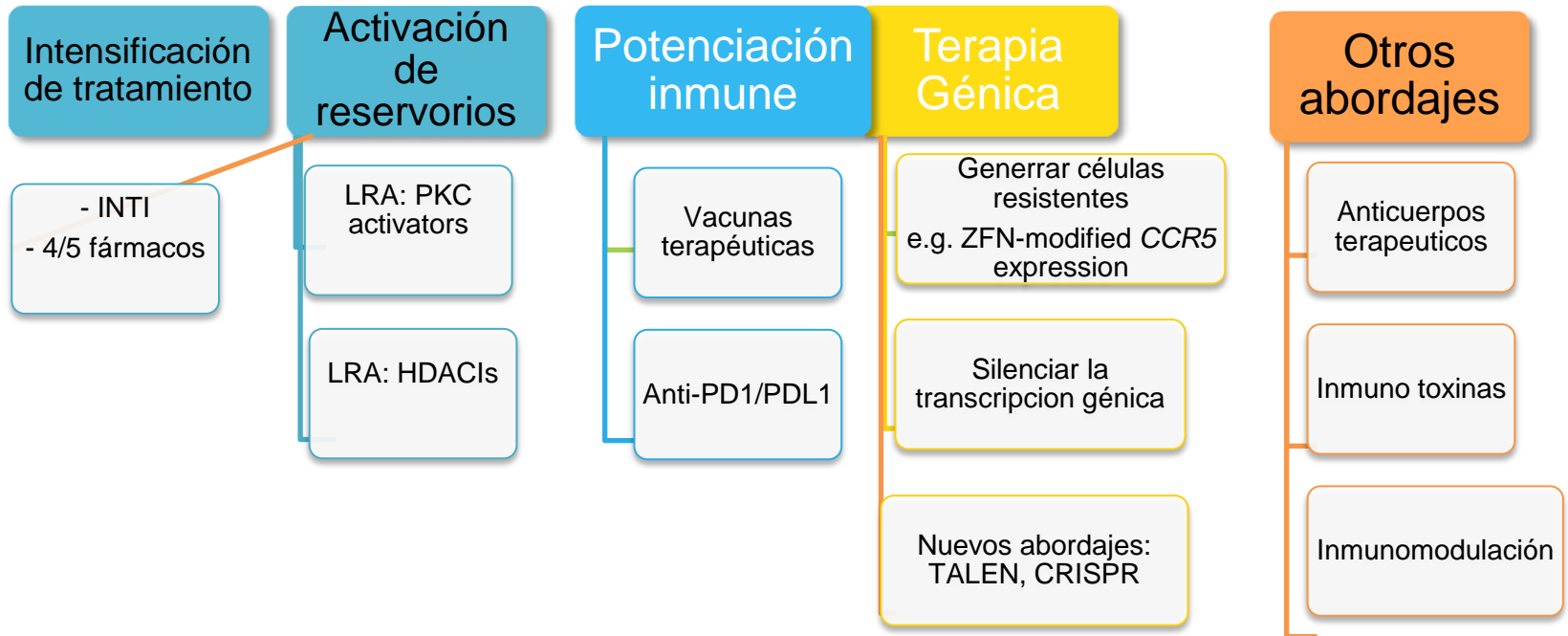
3. Low ongoing replication
• Lymphocyte
• Macrophages

4. Homeostatic proliferation
• IL2
• IL7

5. HIV-induced Clonal expansion

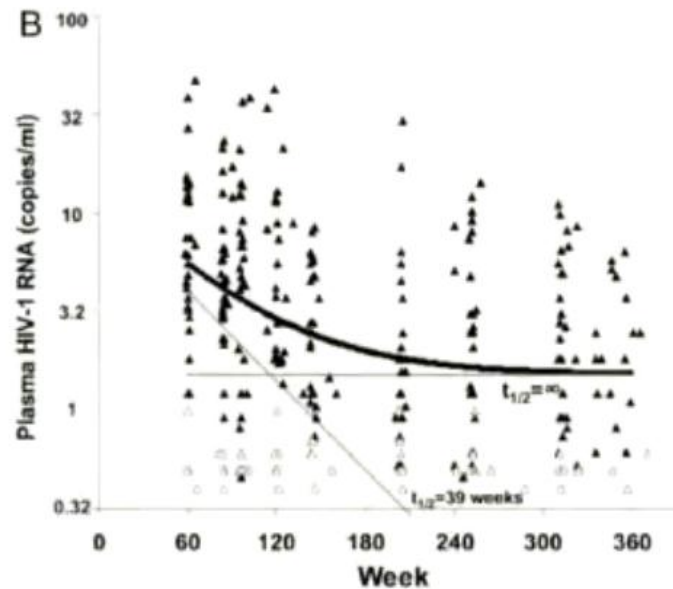


Estrategias para disminuir o eliminar los reservorios.



Pros/Cons for persistent replication during ART

- Residual viremia can be detected by ultrasensitive assays in a majority of individuals on ART

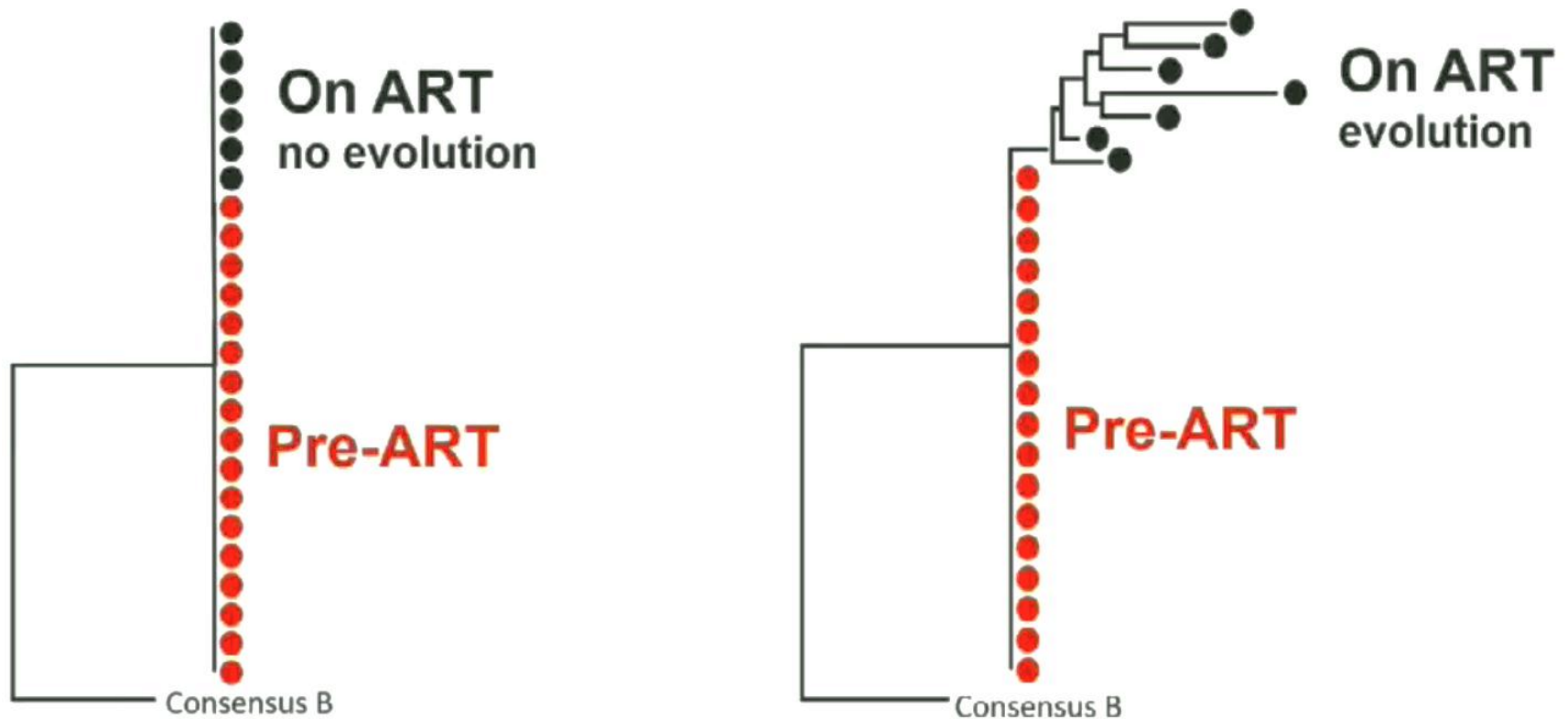


- However, detecting viral particles does not necessarily imply that ongoing replication (complete cycles) occurs: they may reflect only production

A. Sedaghat et al. *PLoS Pathogens* 2007; S. Palmer et al. *PNAS* 2008; M. Mavigneret et al. *PLoS One* 2009; H. Hatano et al. *AIDS* 2010; G. Sahu et al. *J Virol* 2010; J. Anderson et al. *J Virol* 2011; TW. Chun et al. *JID* 2011

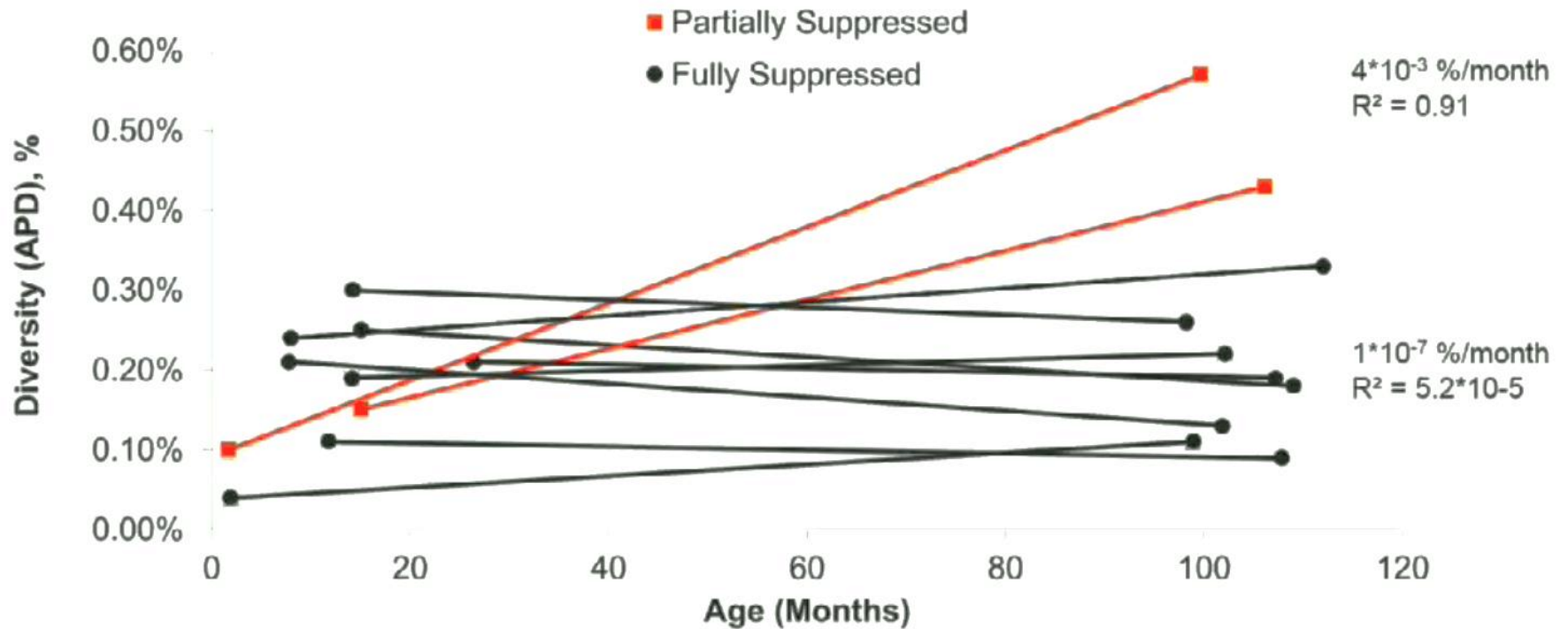
VARIABILIDAD GENETICA Y REPLICACIÓN PERSISTENTE

Investigating HIV Populations on Donors Who Initiated ART in Early Infection Provides Strong Signal to Detect Evolution

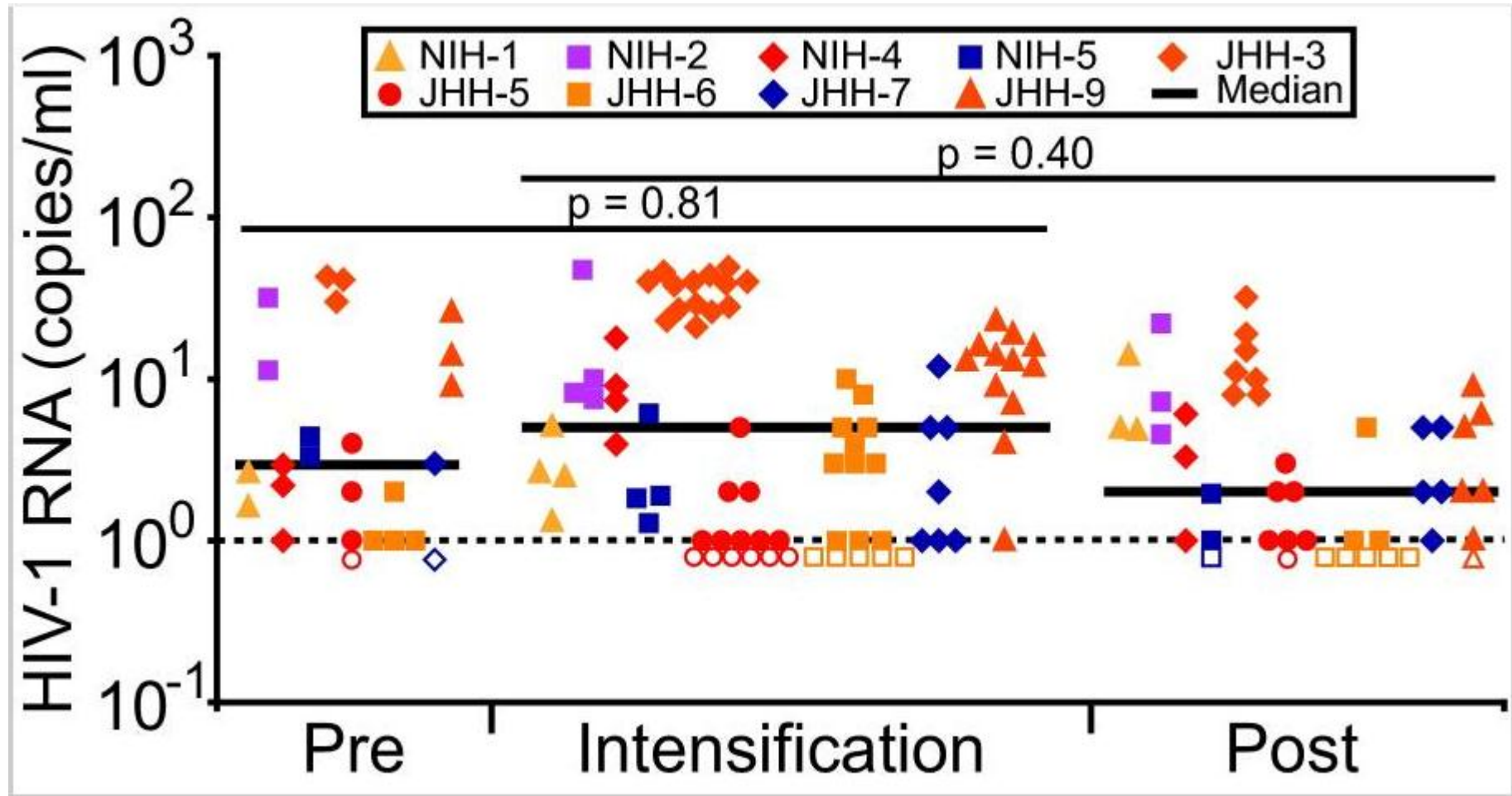


VARIABILIDAD GENETICA Y REPLICACIÓN PERSISTENTE

No Change in HIV Diversity in Babies Fully Suppressed on ART



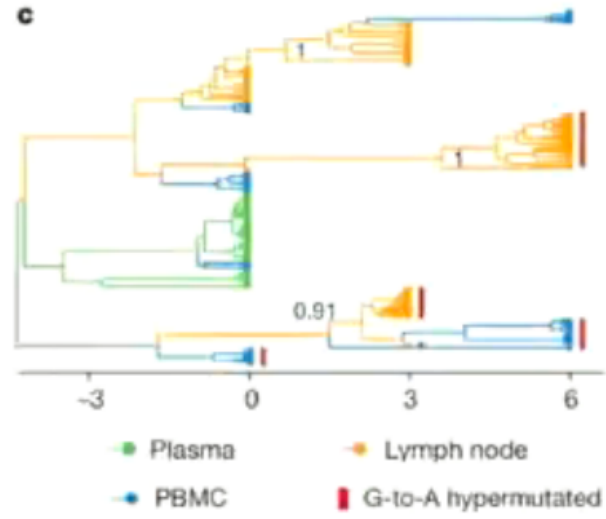
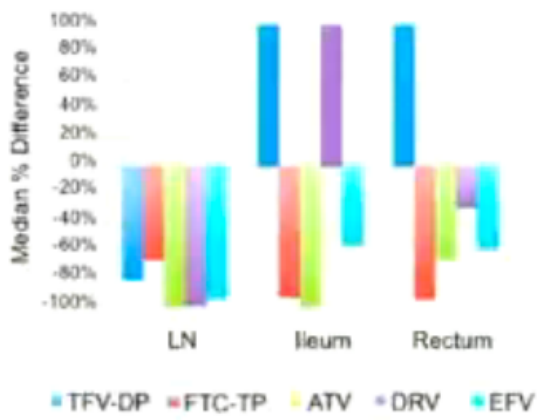
Estrategias para disminuir o eliminar los reservorios.



Pros/Cons for persistent replication during ART

- ART may not diffuse optimally in all tissues
- Some phylogenetic studies suggest that viral evolution may occur in these sites

Median Percent Difference of LT from PBMC Concentrations

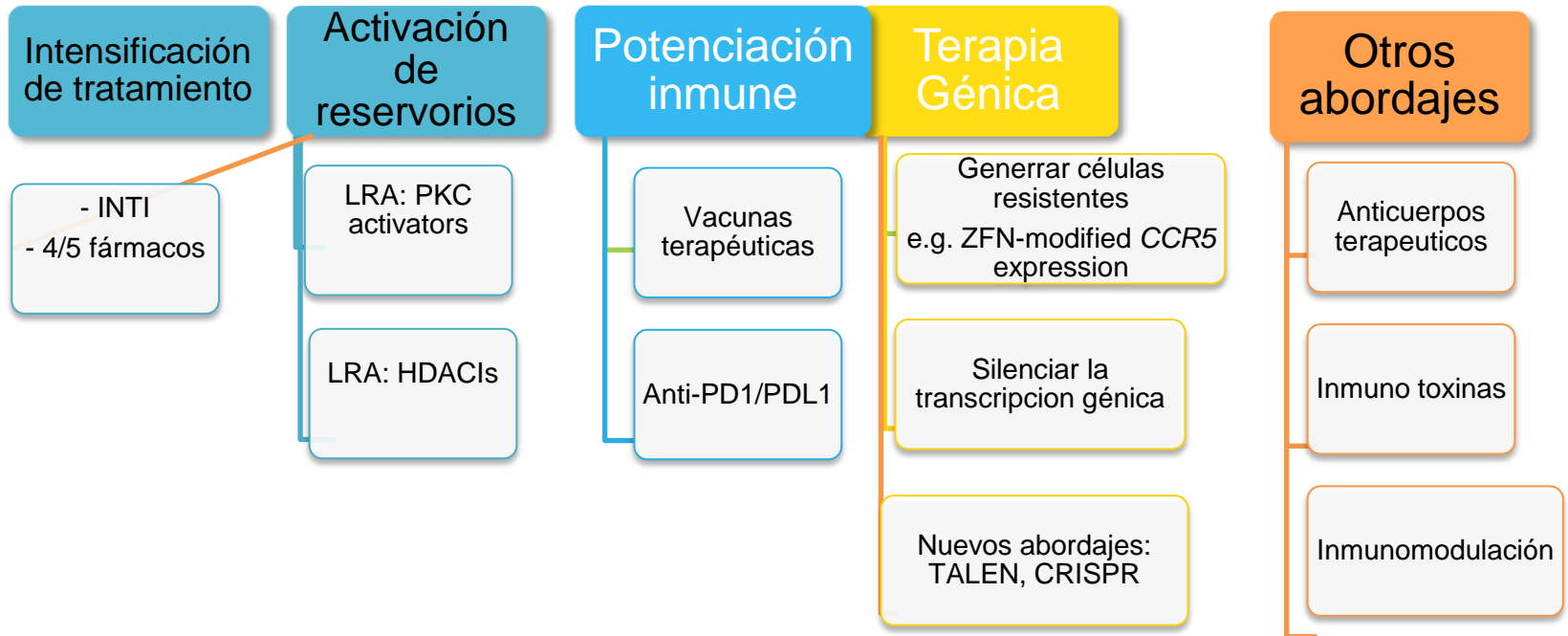


- However, these studies were often conducted in people on relatively short term therapy (6-24 months) and sequencing errors may introduce a bias

LOW ONGOING REPLICATION: THE DEBATE!!!

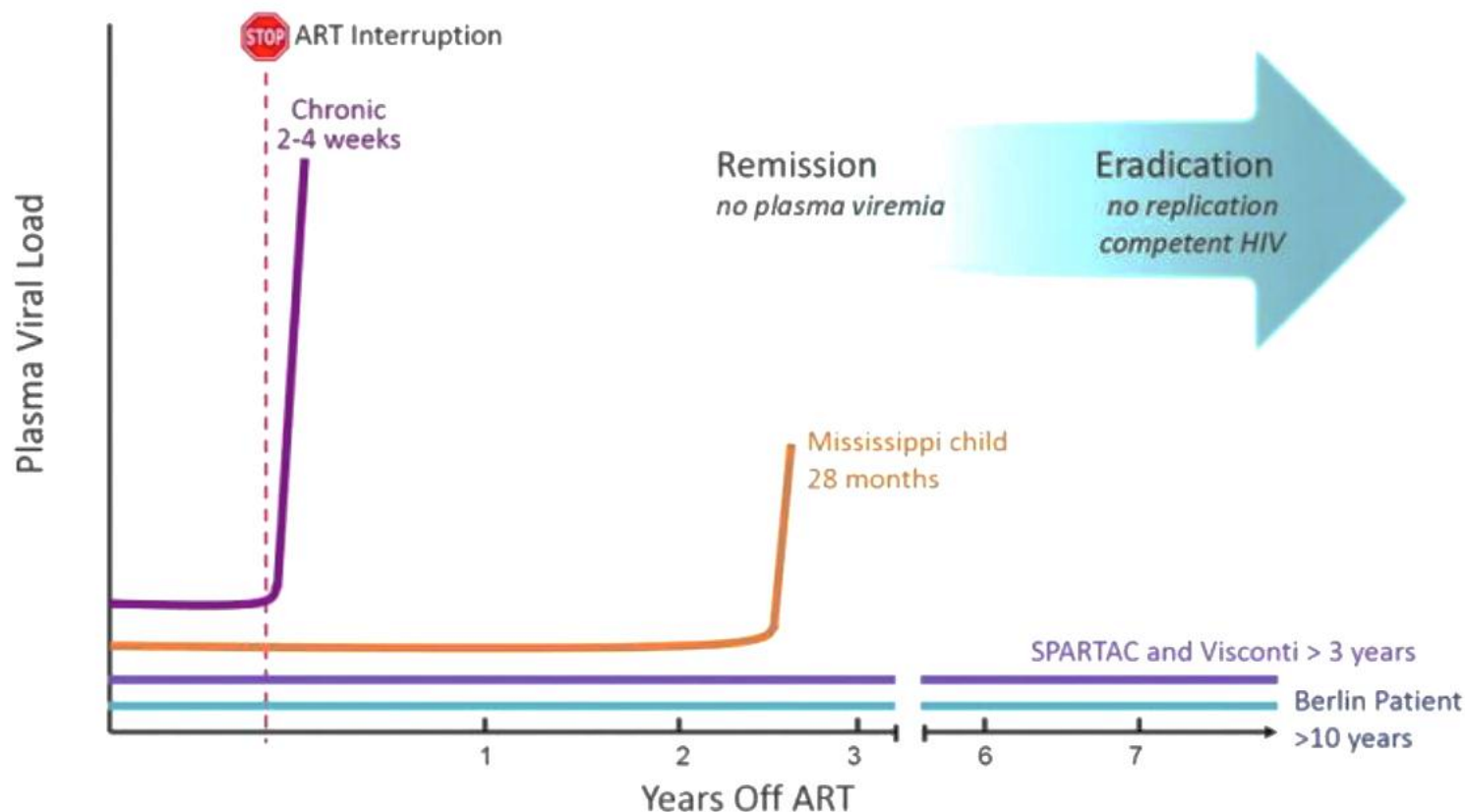


Estrategias para disminuir o eliminar los reservorios.



Tratamiento precoz y control de la infección

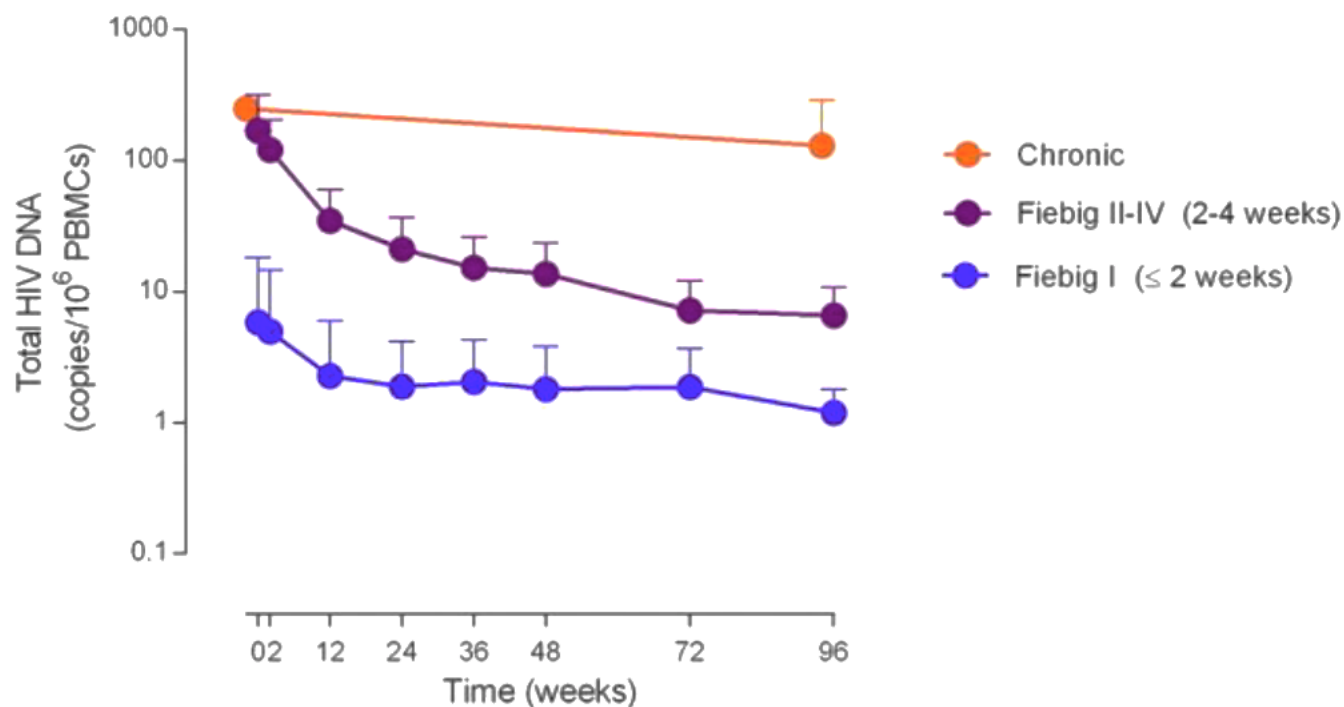
HIV Control Following Treatment Interruption



Hütter, NEJM 2009; Fidler, NEJM 2013; Saez-Cirion, Plos Path 2013; Persaud, NEJM 2013;
Rothenberger, PNAS 2015; Luzuriaga NEJM 2015; Frange, Lancet HIV 2016
Adapted from Cohen, Science 2015; Chomont, IAS 2015 and Deeks, Nature Med 2016

Tratamiento precoz y control de la infección

Significant Decline in HIV Reservoir Size with Early ART

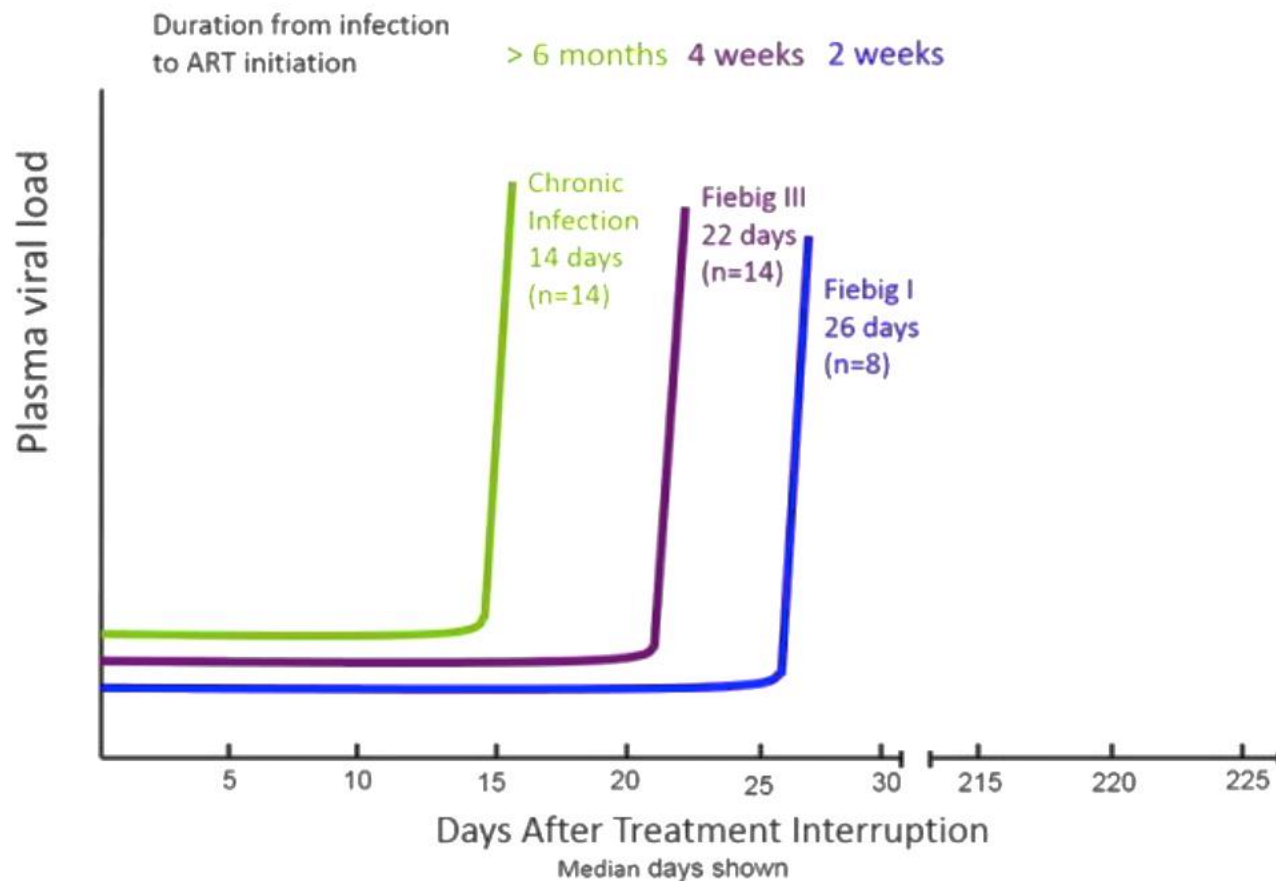


After treatment initiation, in all Fiebig stages there is a rapid decrease in the frequency of cells harboring total HIV DNA, but it remains stable in chronic infection.

Leyre, Chomont, CROI 2017 (948)
RV254 and RV304 Thai studies

Tratamiento precoz y control de la infección

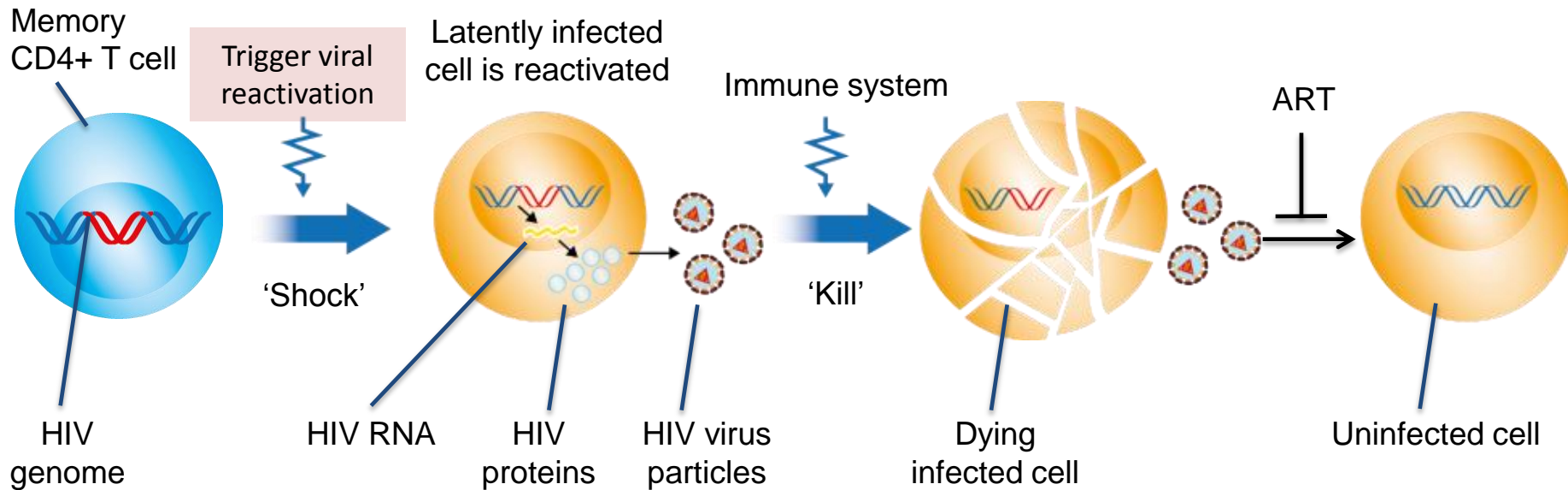
Antiretroviral Therapy: How Early is Early Enough?



Rothenberger, PNAS 2015; Kroon, IAS 2016; Colby, CROI 2017 (852), Timothy Henrich and Steven Deeks (UCSF)

Principios de activación de los reservorios

- Las estrategias de 'Shock and kill' tienen como objetivo la reactivación de virus latentes en presencia de ART para disminuir el tamaño del reservorio

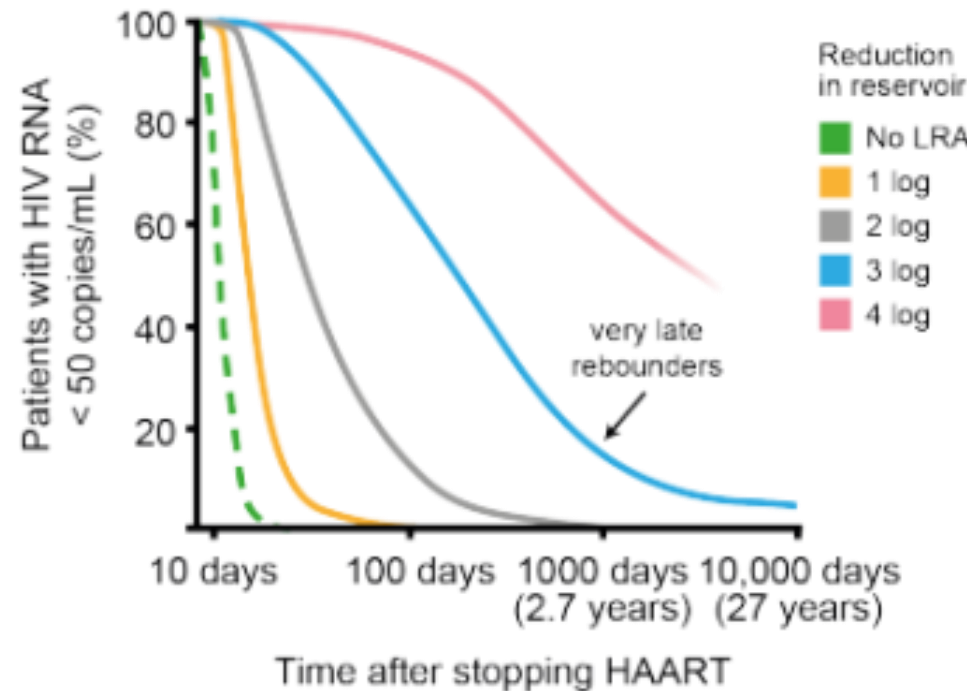
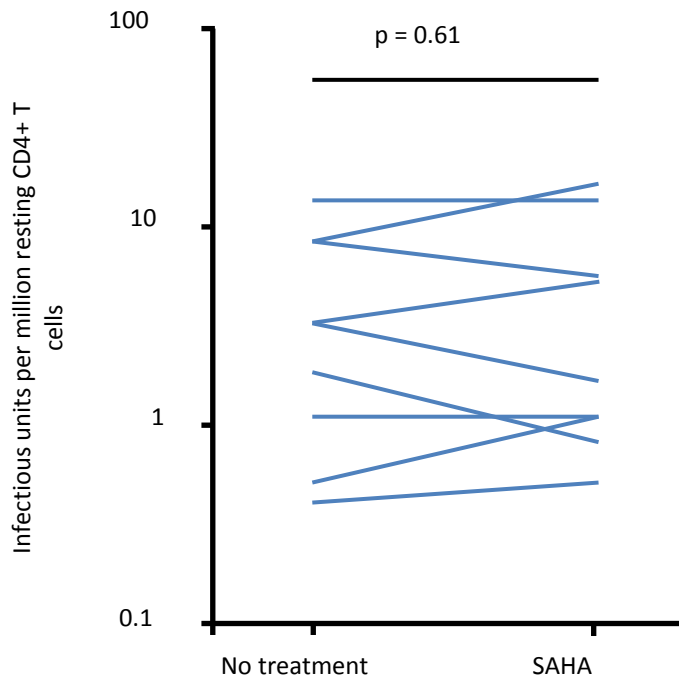


Barreras frente a la curación

Limitaciones de la estrategia de “shock and kill”

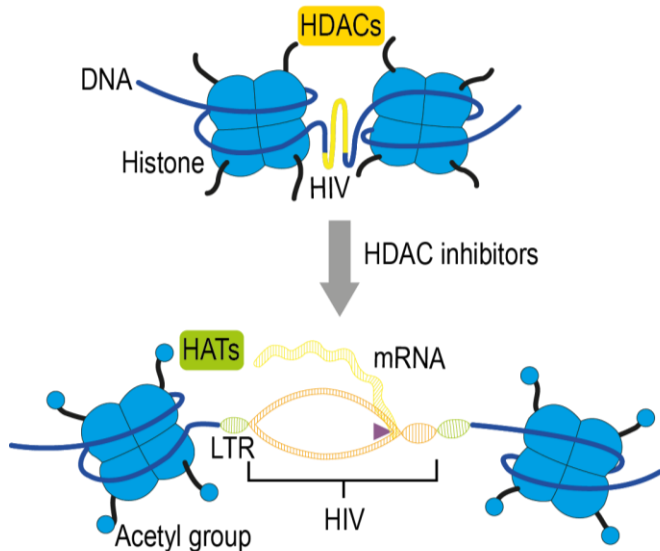
La curación funcional no es posible con los fármacos anti-latencia actuales

1. Los fármacos anti-latencia son poco potentes y no se produce la destrucción por efeto citopático. El reservorio no disminuye
2. Sólo una baja proporción del reservorio es reactivado
3. Los modelos predicen que será necesario disminuir la carga proviral al menos 3 log₁₀ para que exista un impacto clínico significativo



Inhibidores de histona de-acetiladas (HDACs)

- Las HDACs son reclutadas a las histonas donde reprimen la transcripción
- Los inhibidores de HDAC permiten la formación de ADN en forma y el acceso a los factores de transcripción: rompen la latencia



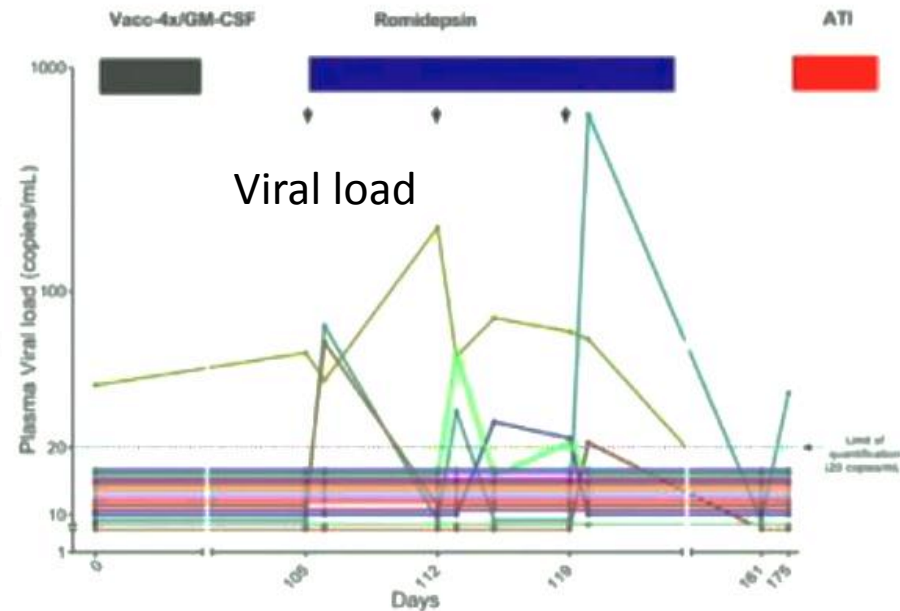
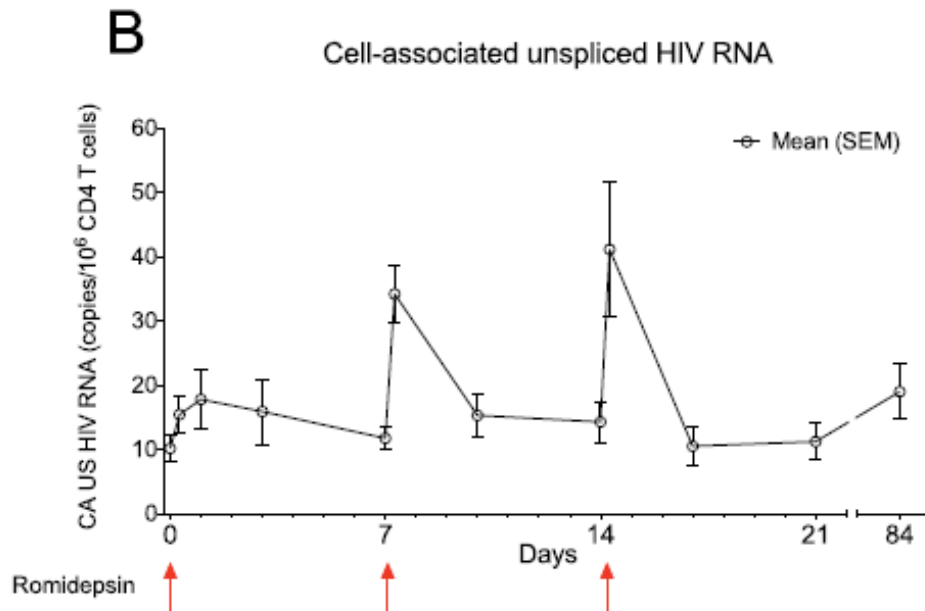
Clinical effects of HDAC inhibitors in aviraemic HIV-infected patients on ART

Pabinostat ^{2,5}	Vorinostat ³	Romidepsin ^{4,5}
<ul style="list-style-type: none"> • Significantly ↑ CA-usRNA levels ($p = 0.003$) • ↑ detection of plasma HIV RNA • Transient ↓ in total HIV DNA • No downregulation of CD8+ response • $n = 15$ 	<ul style="list-style-type: none"> • Initial increase in HIV-1 expression within resting CD4+ T cells • The effect of subsequent doses was much reduced • $n = 5$ 	<ul style="list-style-type: none"> • Induced HIV-1 transcription, resulting in detectable plasma viraemia • No downregulation of CD8+ response • $n = 6$

Figure adapted from Rasmussen TA, et al. Hum Vaccin Immunother 2013;9:790–9. 1. Rasmussen TA, et al. Hum Vaccin Immunother 2013;9:993–1001. 2. Rasmussen TA, et al. CROI 2014; Poster 438LB. Available from: <http://www.croiconference.org/sites/default/files/posters/438LB.pdf>. 3. Archin NM, et al. J Infect Dis 2014;210:728–35. 4. Sogaard OS, et al. IAC 2014; Presentation TUA0106LBOleson et al, CROI 2015; Poster 369.

Romidepsina induce la reactivación del VIH

- Proof-of-concept phase Ib/IIa trial²
- Six aviraemic HIV-1 infected adults received intravenous 5 mg/m² romidepsin once weekly for three weeks while maintaining ART²

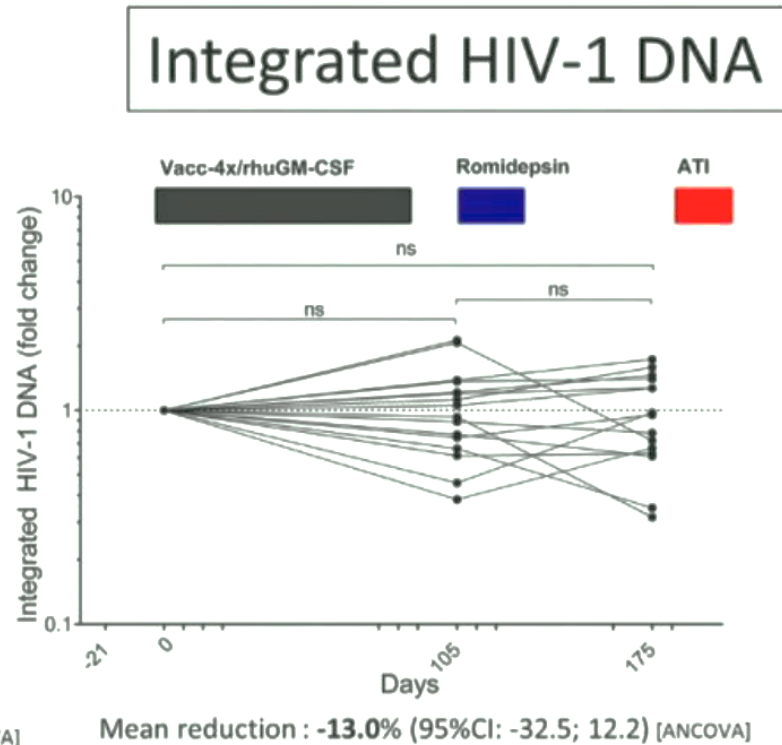
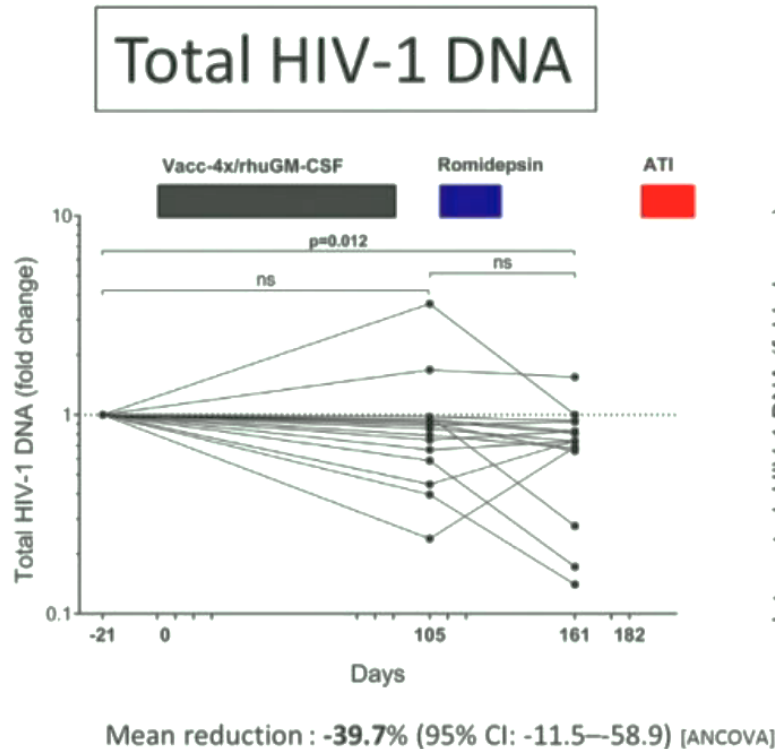


- Romidepsin safely induced HIV-1 transcription²
- Reversal of HIV-1 latency *in vivo* is possible without blunting T cell-mediated immune responses²

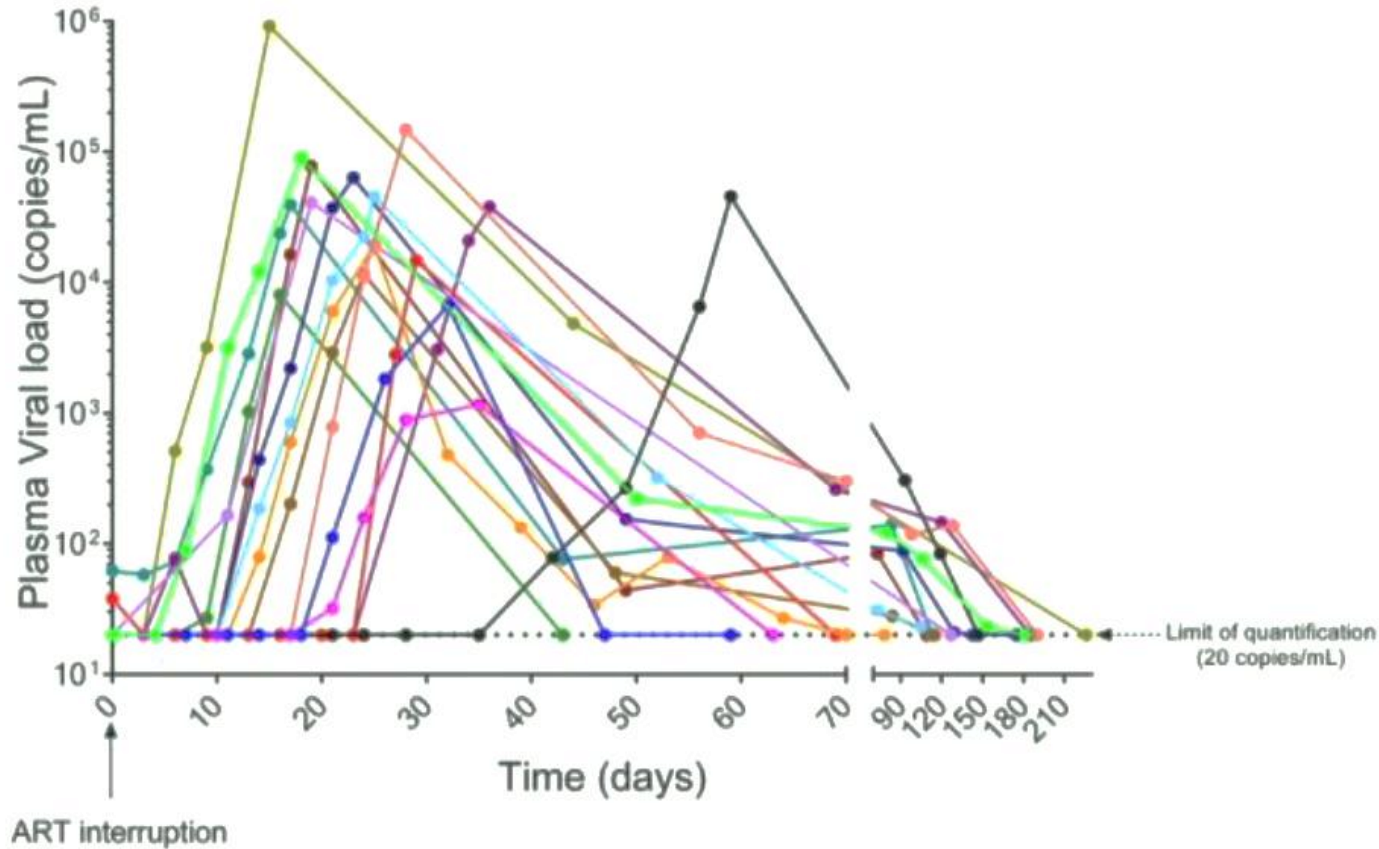
ART, antiretroviral therapy

1. Oleson et al, CROI 2015; Poster 369.
2. Sogaard O, et al. PLOS Pathog 2015;11(9):e1005142.

Impacto de Romidepsina en el ADN proviral



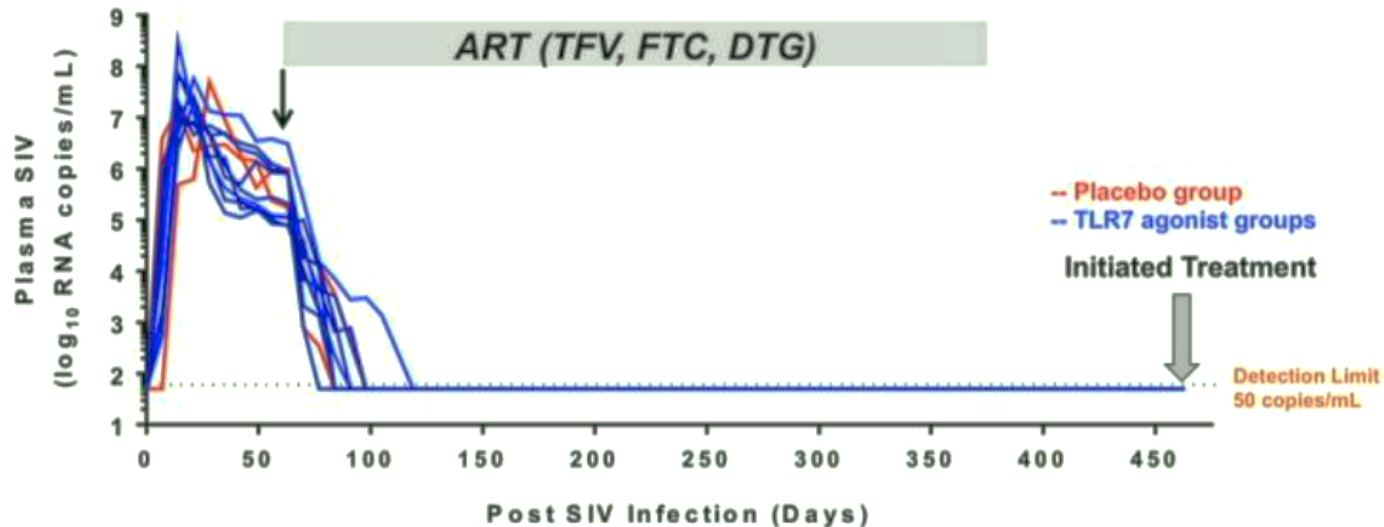
Impacto de Romidpesina en el tiempo hasta el repunte viral tras una interrupción terapéutica



Median time to VL >50 c/mL: 14 days

Agonistas de TLR7

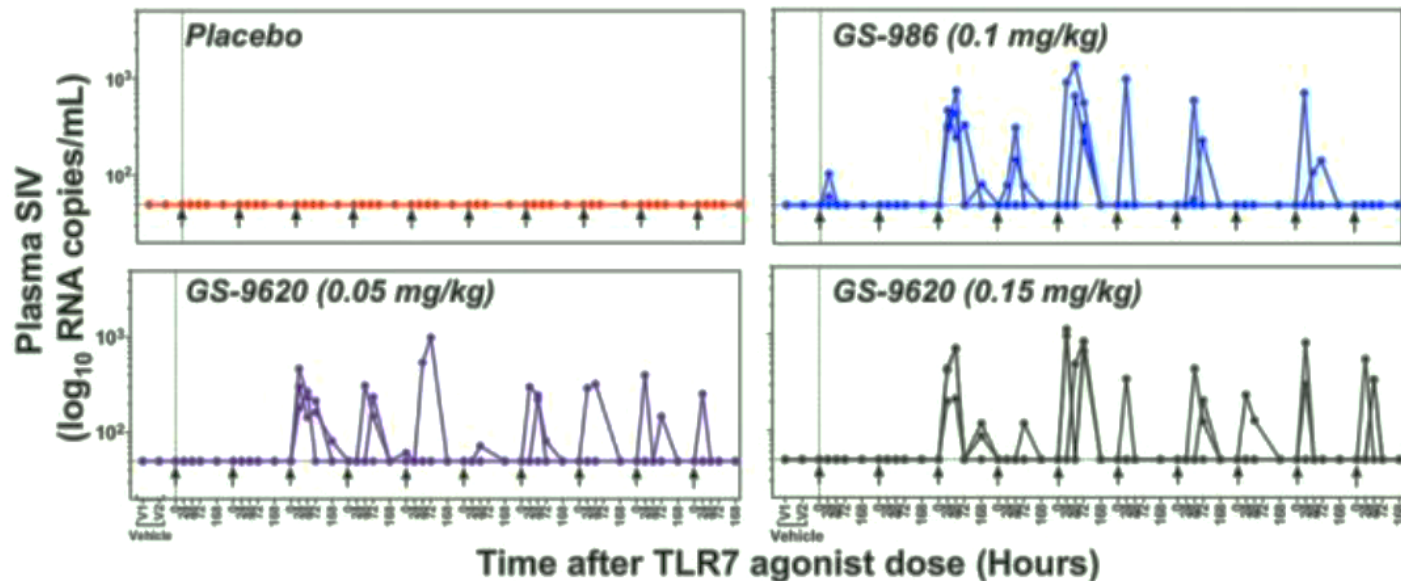
Effective ART in SIV-infected Rhesus Monkeys



- Placebo and TLR7 agonist treatment groups are similar in:
 - total viral burden pre-ART
 - mean plasma SIV RNA levels at initiation of ART
 - time to viral suppression (SIV RNA <50 copies/mL) on ART

Agonistas de TLR7

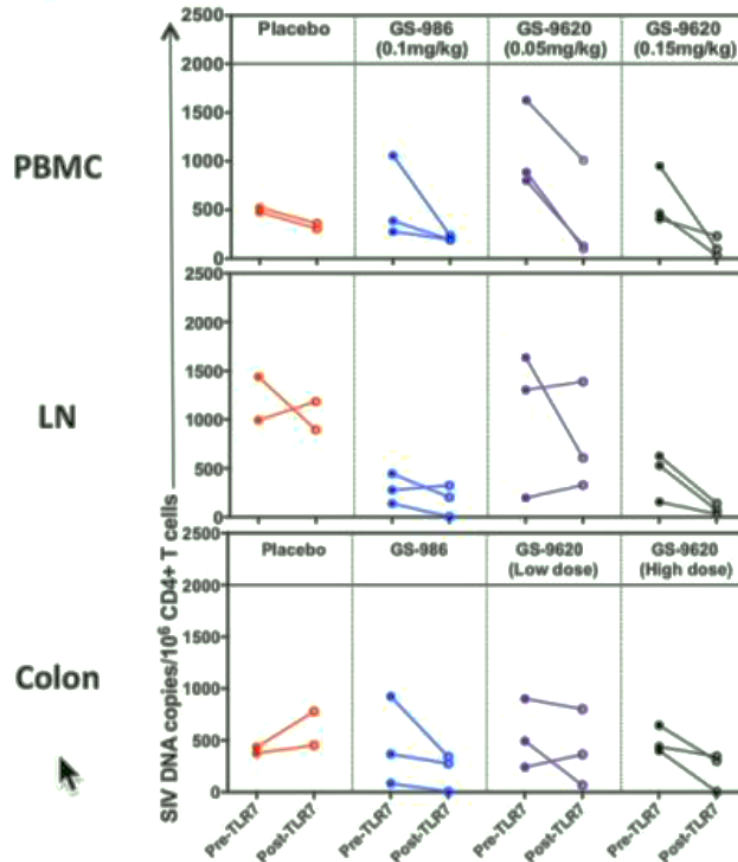
TLR7 Agonists Induce Transient Plasma Viremia



- Reduced frequency of blips 38-75% (doses 3-10)
- No additional blips from animals dosed after 3 month pause (doses # 11-19)

Agonistas de TLR7

SIV DNA Levels Reduced in Memory CD4+ T cells from TLR7 Agonist Treated Monkeys on ART



- More pronounced decreases in viral DNA levels in TLR7 agonist treated animals as compared to placebo

Agonistas de TLR7

Plasma SIV RNA Rebound after Stopping ART

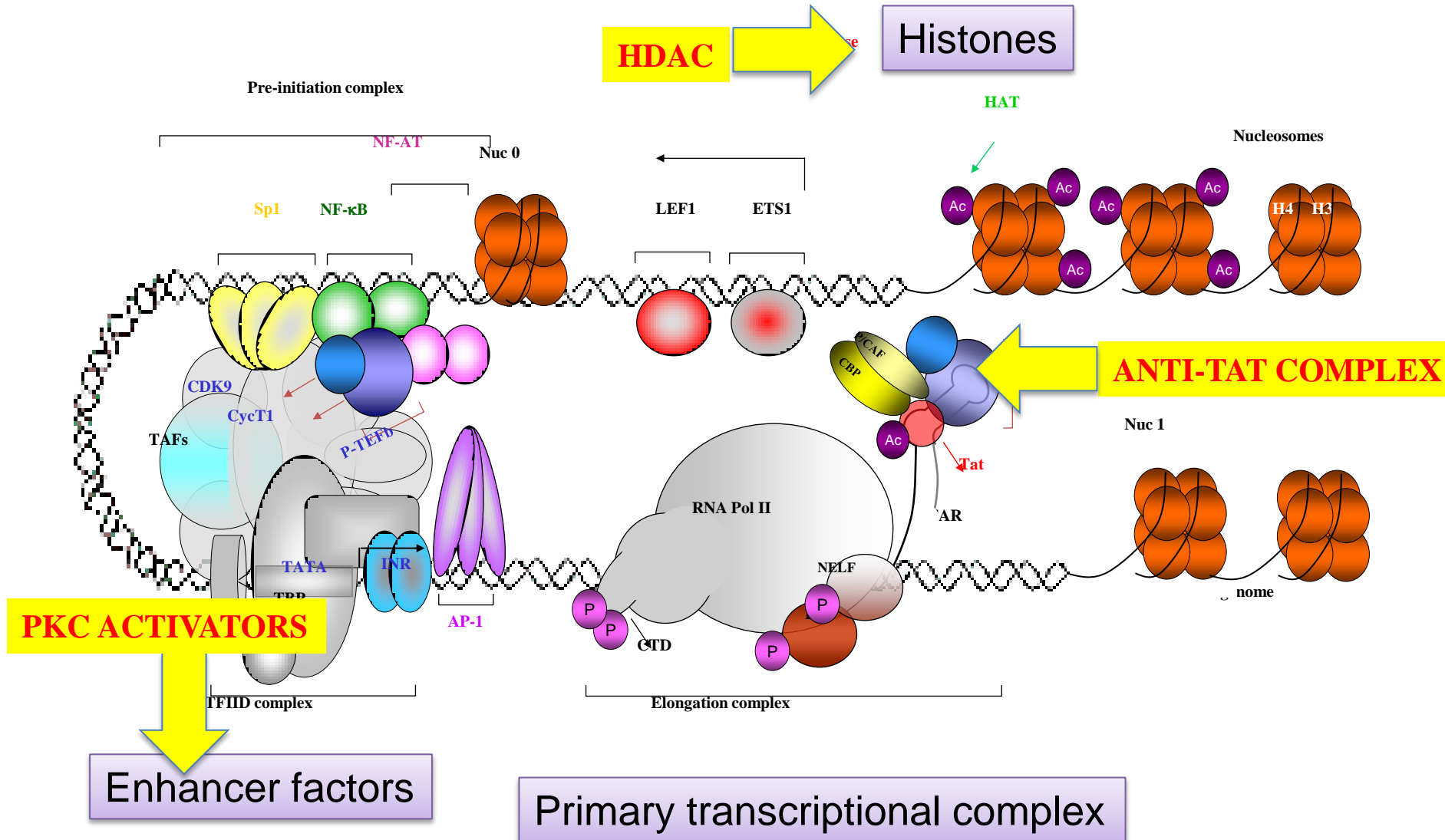


FASE I EN HUMANOS EN DESARROLLO

- 2 of 9 animals treated with TLR7 agonists have undetectable plasma virus up to 3-4 months off ART.
- Same 2 animals with no ConA-inducible virus in PBMC and inguinal LN cultures.

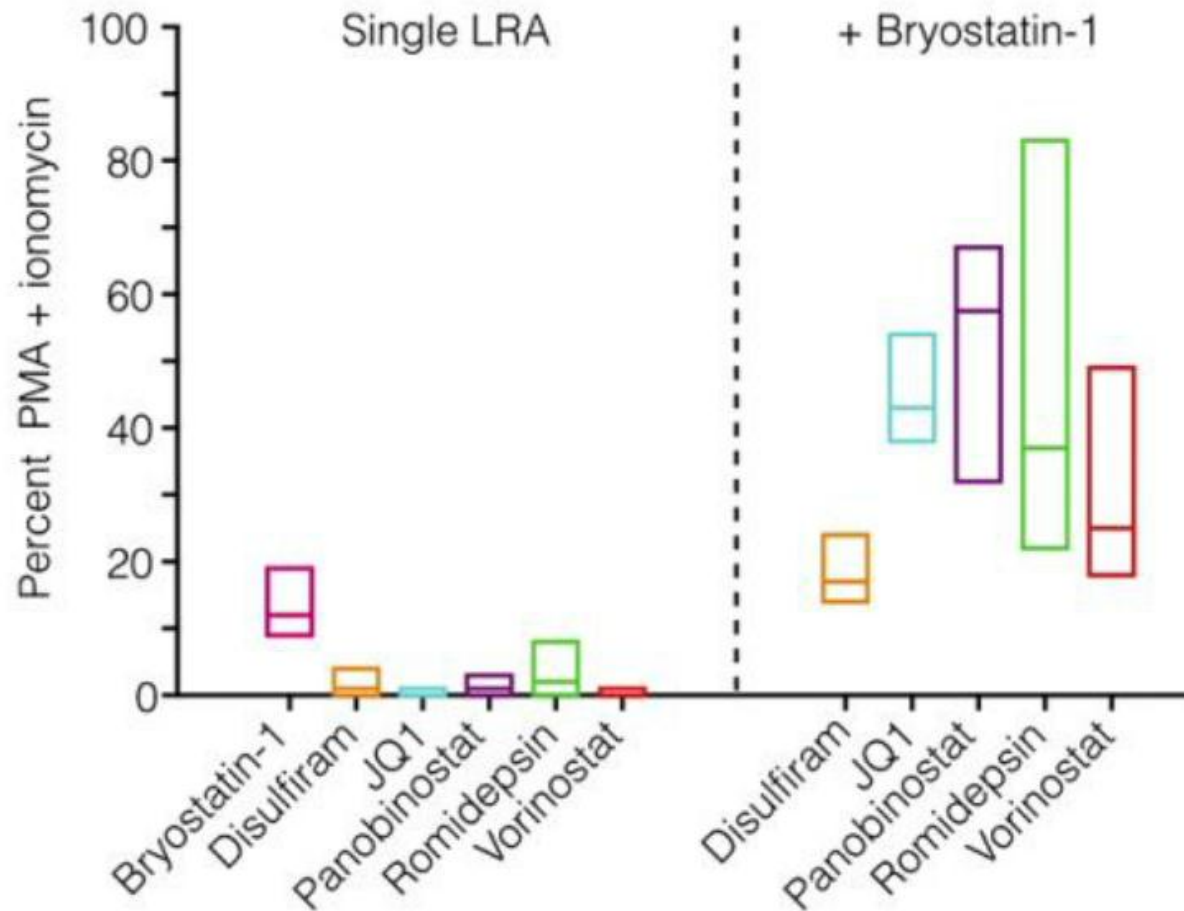
Nuevas estrategias.

Combinación de fármacos anti-latencia

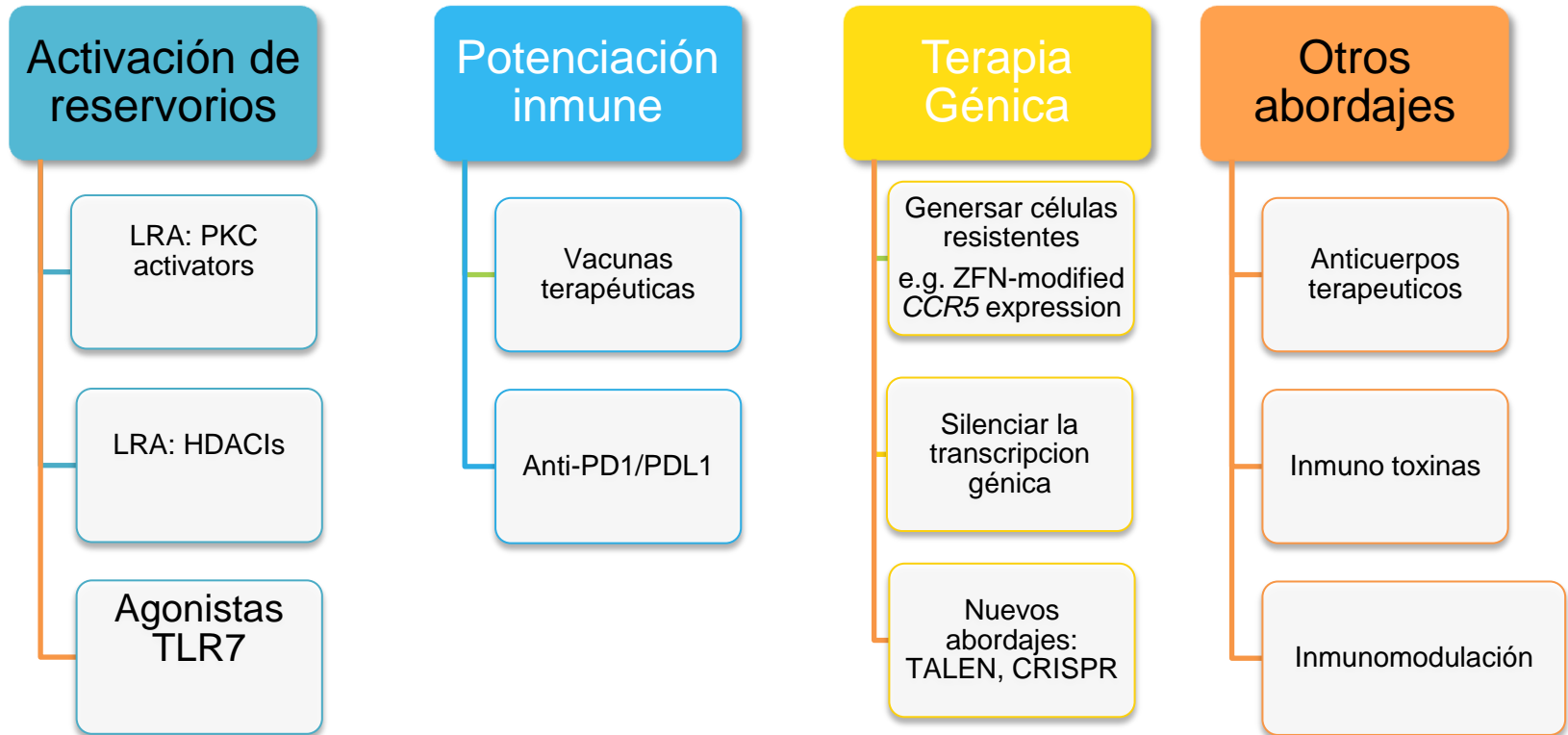


Nuevas estrategias.

Combinación de fármacos anti-latencia

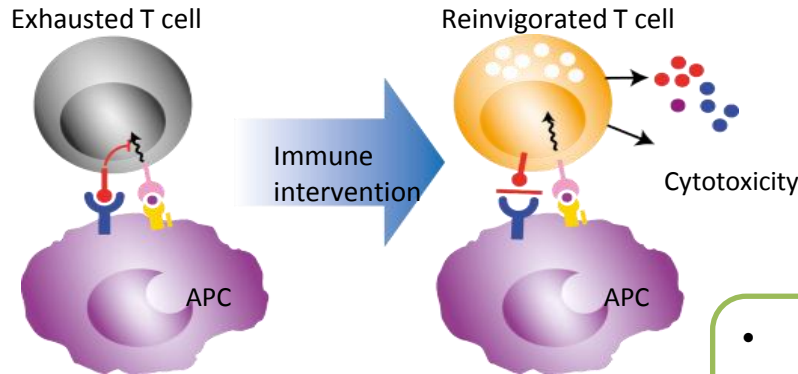


Estrategias para disminuir o eliminar los reservorios.

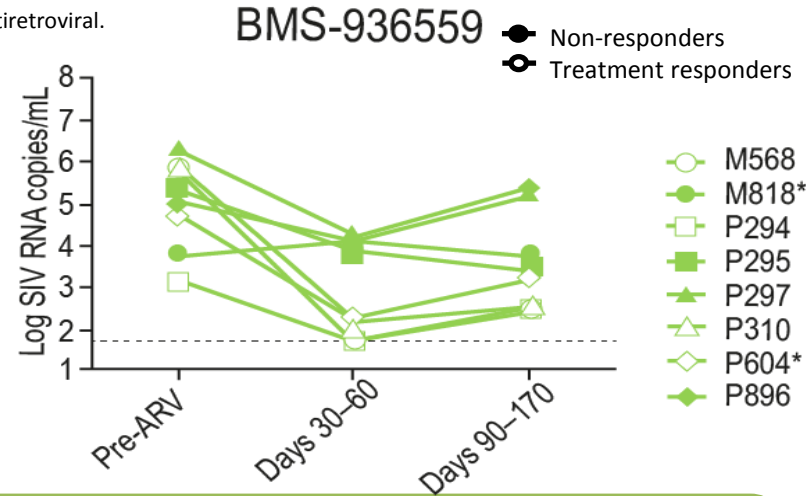


Inmunopotenciación con anti-PD-L1

PD-1 es un inhibidor de la activación inmune que se expresa con mayor frecuencia en linfocitos latentemente infectados: potenciador inmune + efecto sobre el reservorio (?)



*Mamu*A01.
ARV, antiretroviral.

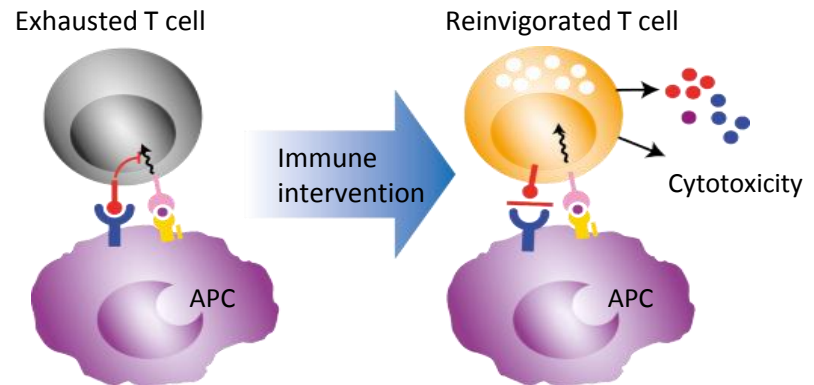


- El tratamiento con un anticuerpo anti-PD-L1 (BMS-936559) produjo la supresión viral tras interrumpir el tratamiento en macacos infectados.

Trial	Current status
NCT02028403 Randomised phase I trial	<ul style="list-style-type: none"> Following pilot phase I study,³ double-blind trial of BMS-936559 at 0.3, 1.0 and 3.0 mg/kg initiated in HIV in conjunction with the AIDS Clinical Trials Group (ACTG-5326)⁴ Participant recruitment to this study is currently on hold⁵

Inmunopotenciación con anti-PD-L1

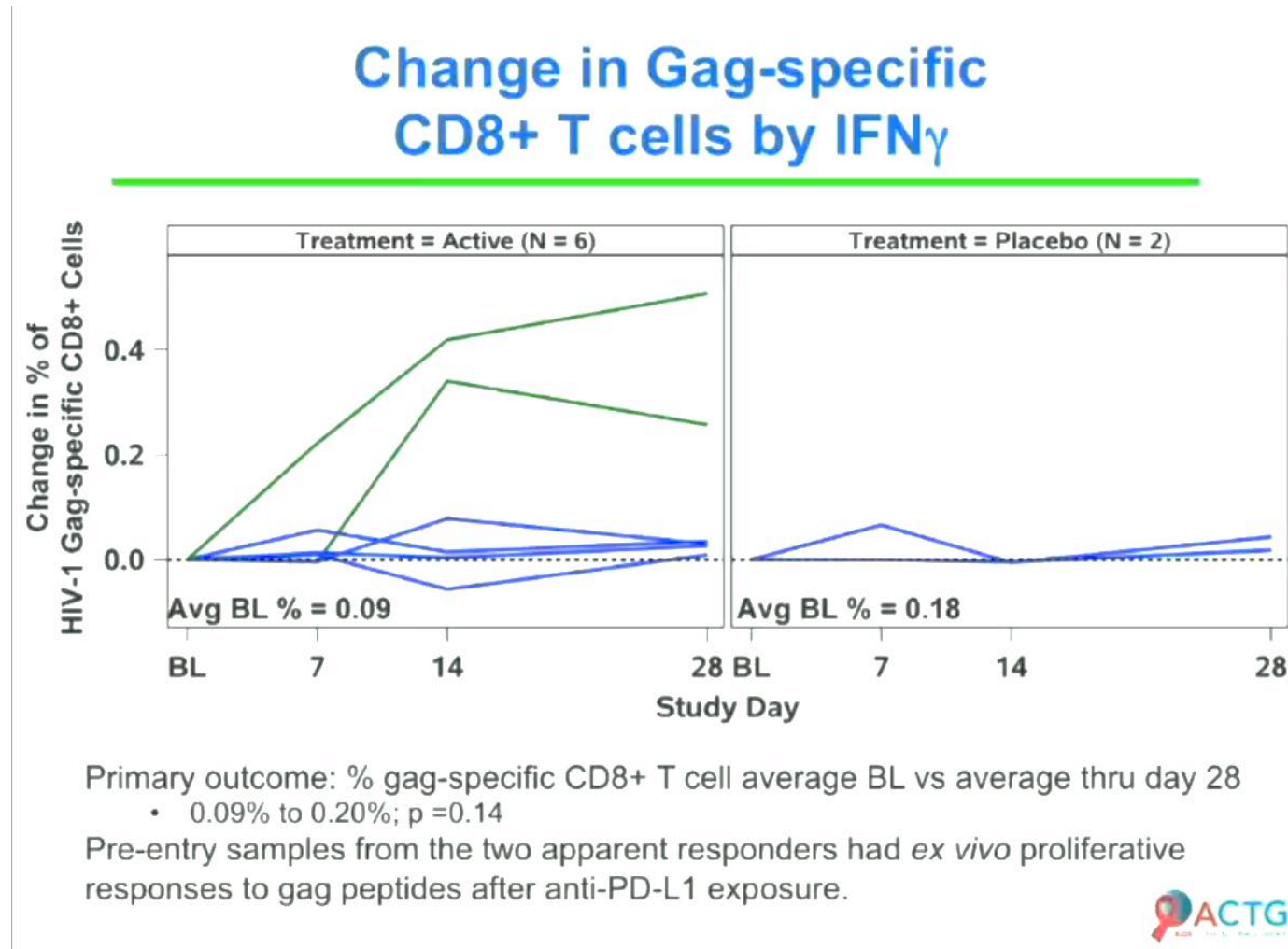
Generate de novo or boost pre-existing HIV-specific T-cell responses



Study Design

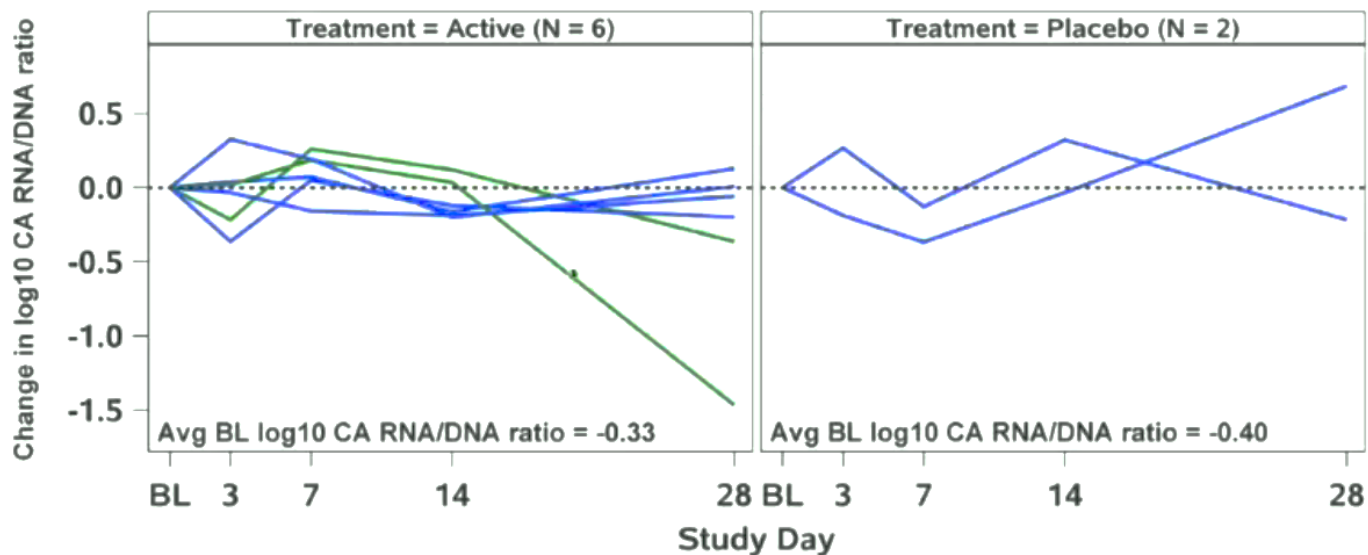
- Phase I, double-blind placebo*-controlled study of single dose infusions of BMS-936559 with 4 sequential dose-escalating cohorts
 - Cohort 1 will receive 0.3 mg/kg IV or placebo
 - Cohort 2 will receive 1 mg/kg IV or placebo
 - Cohort 3 will receive 3 mg/kg IV or placebo
 - Cohort 4 will receive 10 mg/kg IV or placebo

Inmunopotenciación con anti-PD-L1



Inmunopotenciación con anti-PD-L1

Change in HIV-1 cell-associated RNA to DNA Ratio



- Single participant had 10-fold decline in CA-HIV RNA
- No change in median cell associated RNA/DNA ratio over 28 days



Inmunopotenciación con anti-PD-L1

Adverse Events (blinded assessments)

- 36 weeks post-infusion, an asymptomatic participant with previously normal cortisol levels had a low AM level and was subsequently diagnosed with hypoadrenalism and hypogonadism thought secondary to hypophysitis

Subsequently unblinded and received active anti-PD-L1

- Enrollment halted after first cohort

Retinal toxicity noted in 3-month animal study

To date, no evidence of similar findings in study participants

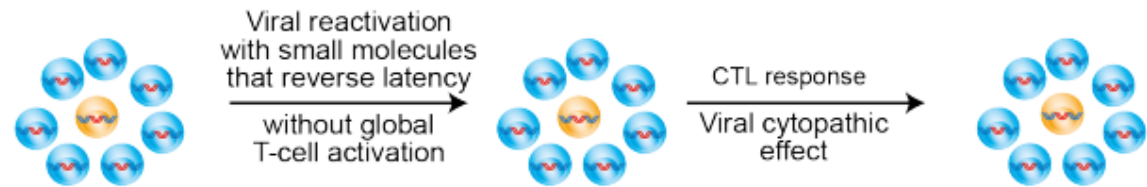


Inmunopotenciación

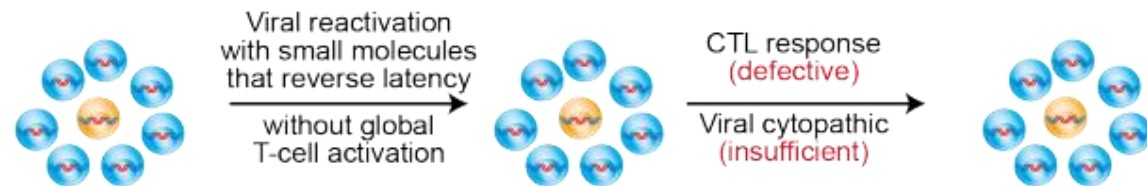
Combinación de fármacos anti-latencia y vacunas para reactivar y destruir los reservorios

Necesitamos un sistema inmune plenamente competente para conseguir la curación

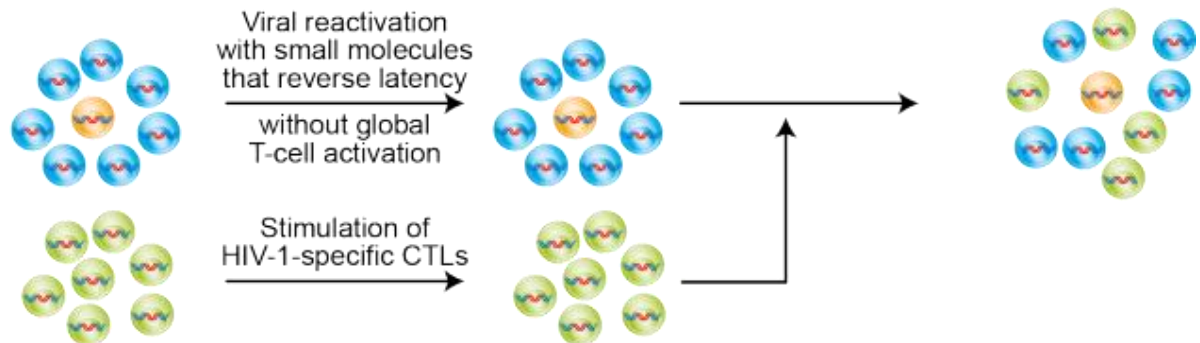
Previous hypothesis



Our findings



Our solution



- Resting CD4⁺ T cells
- Latently infected resting CD4⁺ T cells
- CD8⁺ T cells

Viral control induced by HIVCONSV vaccines and romidepsin in early-treated individuals

Study Participants

n=15

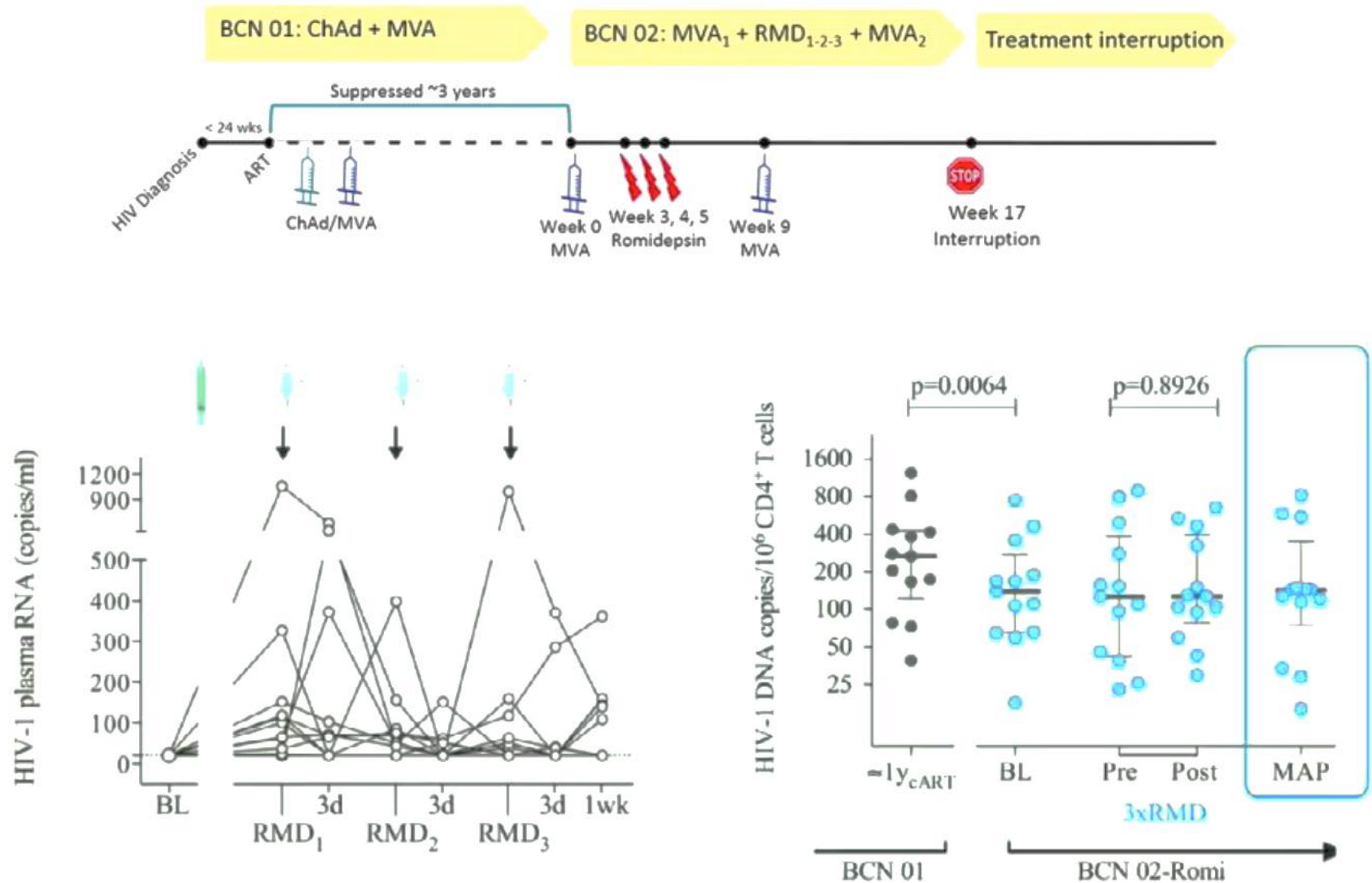


Age at study entry, median (range)	43 (33 - 51) y.o.
Days since HIV to cART, median (range)	92 (28 - 164) days
Pre cART Log ₁₀ HIV-1 RNA copies/ml, median (range)	4.9 (3.2 - 5.8) log ₁₀ cp/ml
Years on cART median (range)	3.23 (3.03 - 3.77) years
cART, n (%)	
TDF/FTC/RAL	11 (73%)
ABC/3TC/RAL	2 (13%)
ABC/3TC/DTG	2 (13%)
CD4+ T-cell counts at study entry, median (range)	728 (416 - 1,408) cells/mm ³
Ratio CD4/CD8 at study entry, median (range)	1.37 (0.97 - 1.93)

Mothe B. et al, BCN 02
CROI 2017 - 119LB



Combination Latency Reversing Agent (Romidepsin) and Therapeutic Vaccine (HIVconsv)

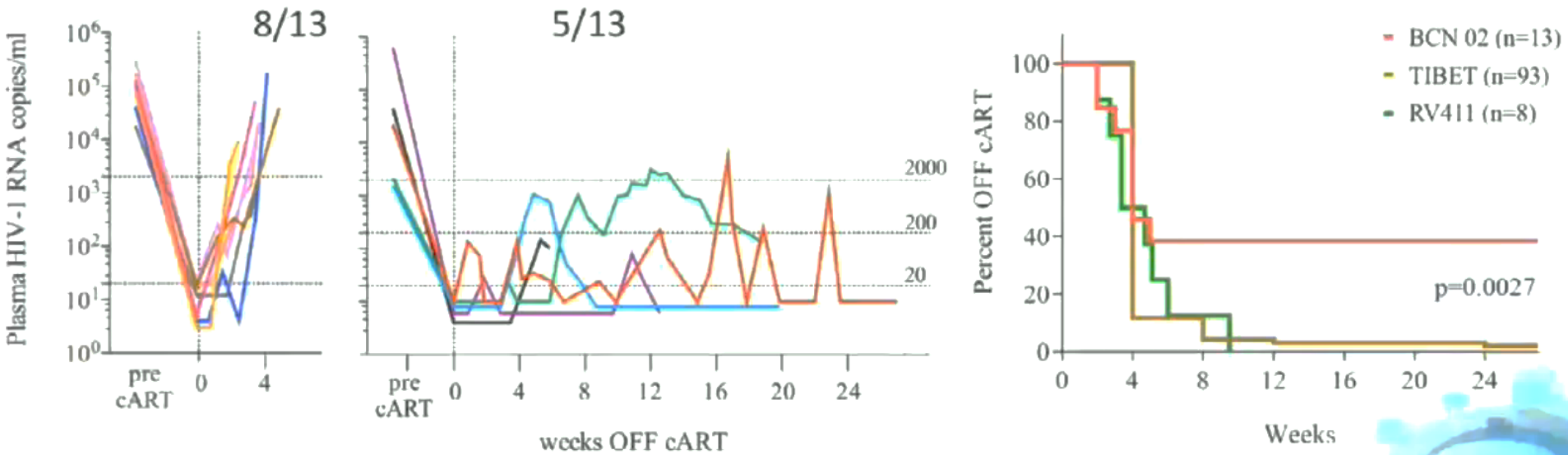


Monitored Antiretroviral Pause (MAP)

n=13

Feb 15th

- 13 participants have interrupted cART to date.



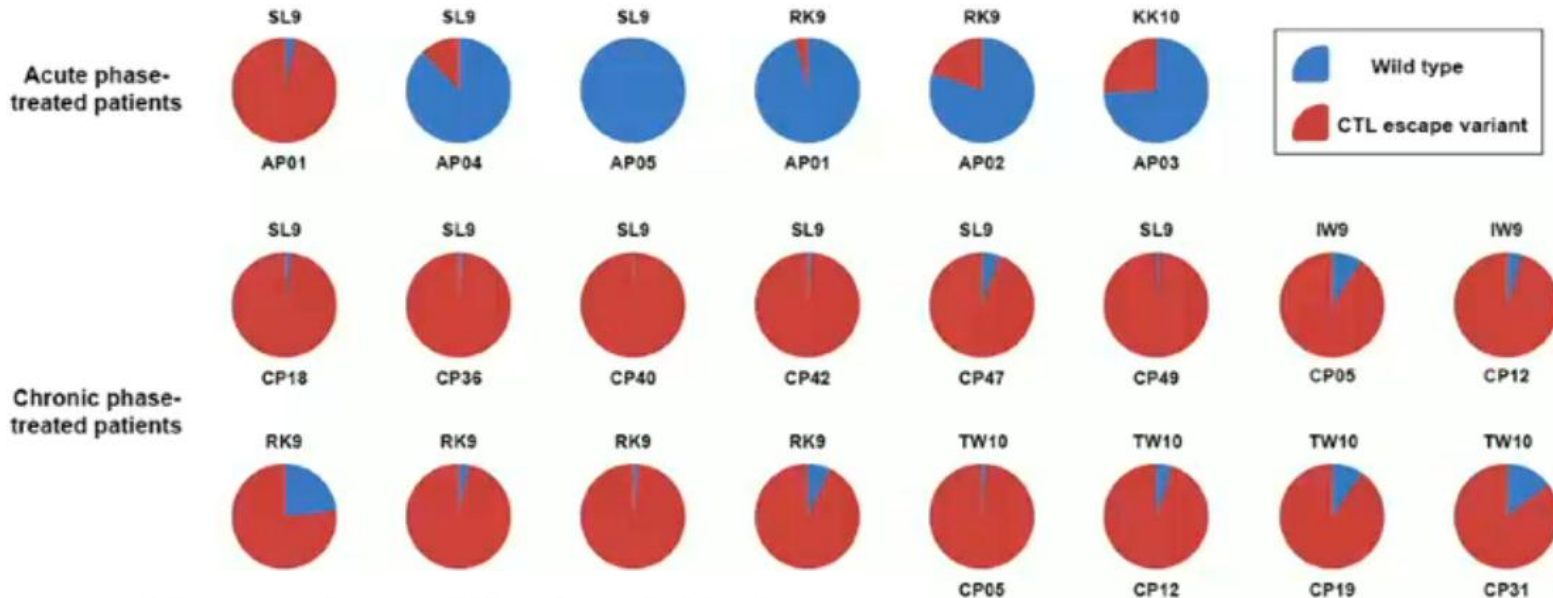
¹⁵Ruiz, 2007; ¹⁶Colby, #124; ¹⁶Leal, #336; ¹⁷Genevieve, 2017; ¹⁸Saez-Cirian, 2013; ¹⁹Rosenberg, 2010; ²⁰Cockerhan, 2016

Mothe B. et al, BCN 02
CROI 2017 - 119LB

Inmunopotenciación

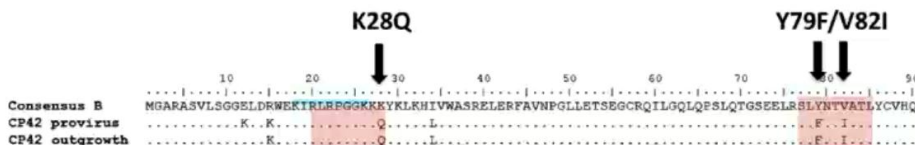
Combinación de fármacos anti-latencia y vacunas para reactivar y destruir los reservorios. Limitaciones

CTL escape variants dominate in the latent reservoir of chronic phase but not acute phase-treated patients

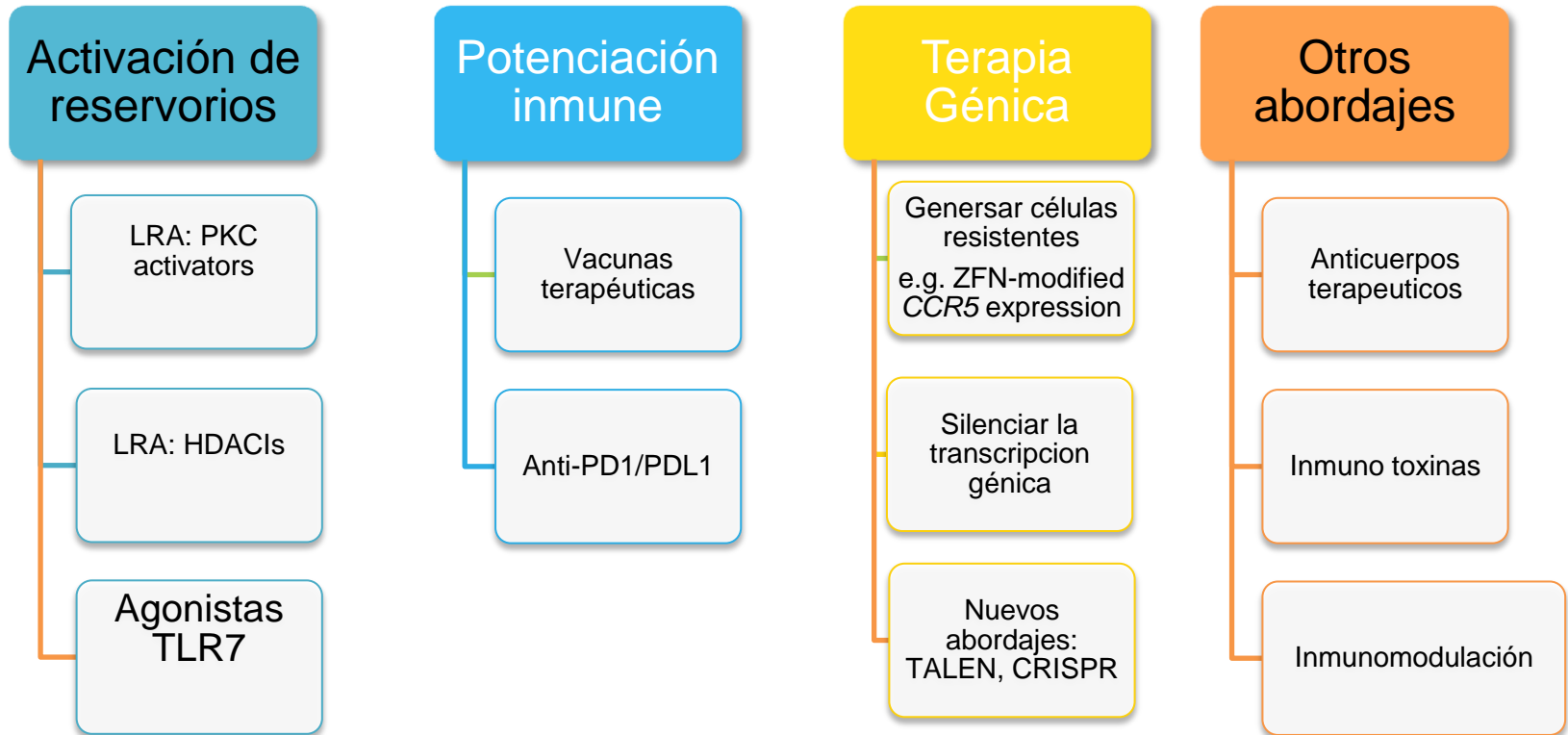


CTL escape variants would be released by latently infected cells after viral reactivation

We will need CTL-based therapeutic vaccines targeting both dominant and subdominant epitopes



Estrategias para disminuir o eliminar los reservorios.



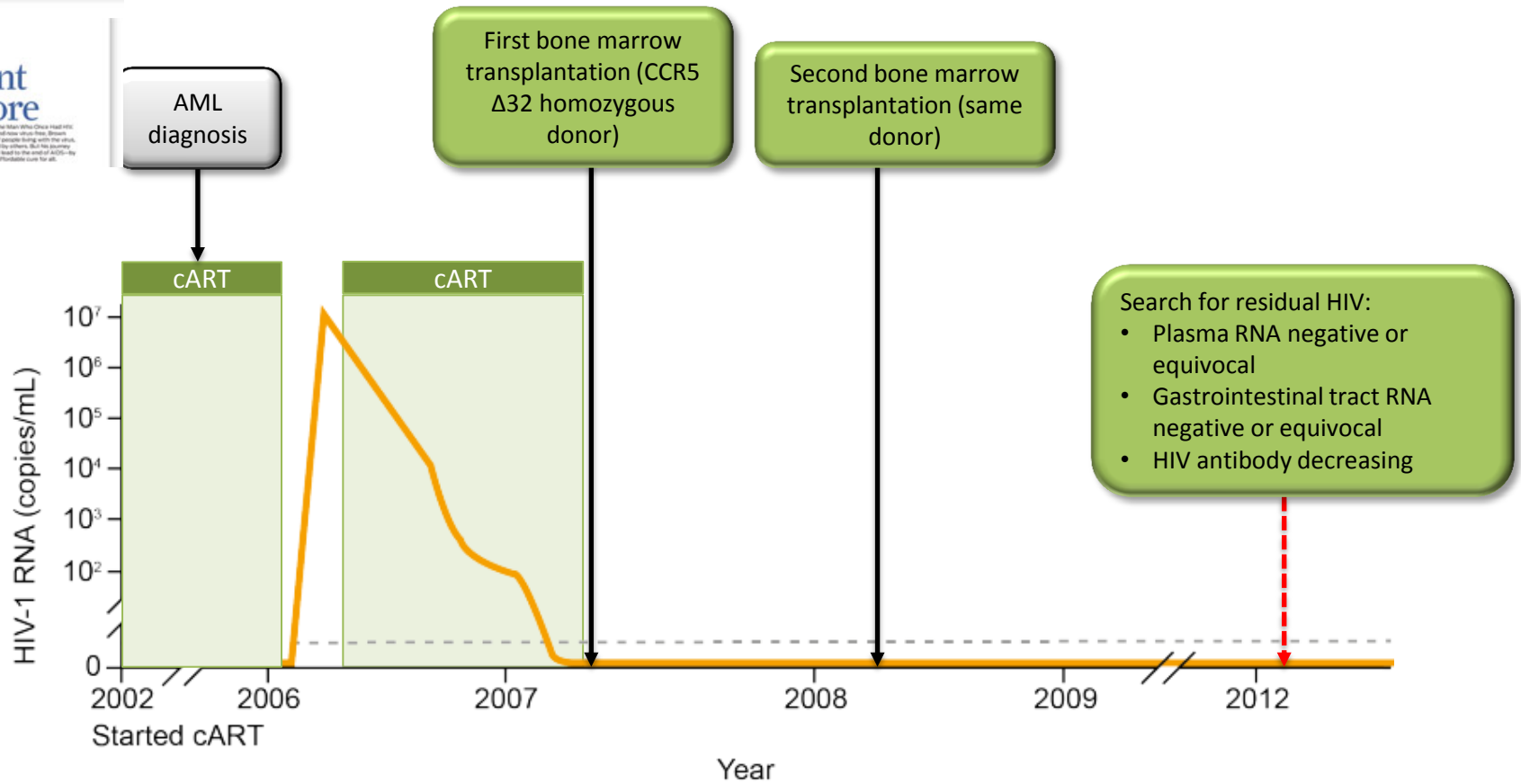


El paciente de Berlín: la prueba de concepto de que la curación es posible ¿Excepción o realidad?

Timeline for the Berlin patient: the first and longest duration clinical cure case

----- Limit of detection in tests used after transplantation (1 copy/mL)

Patient No More
Timothy Brown—U.S.A. “The Berlin Patient”—is the first man who has been measured from a deadly form of leukemia and now virus-free. Brown embodies the hopes of scientists and doctors of curing living with the virus. Brown’s case is a rare anomaly. It is not intended to suggest that the cure is a cure for all. It is not intended to suggest that the cure is a cure for all. It is not intended to suggest that the cure is a cure for all.

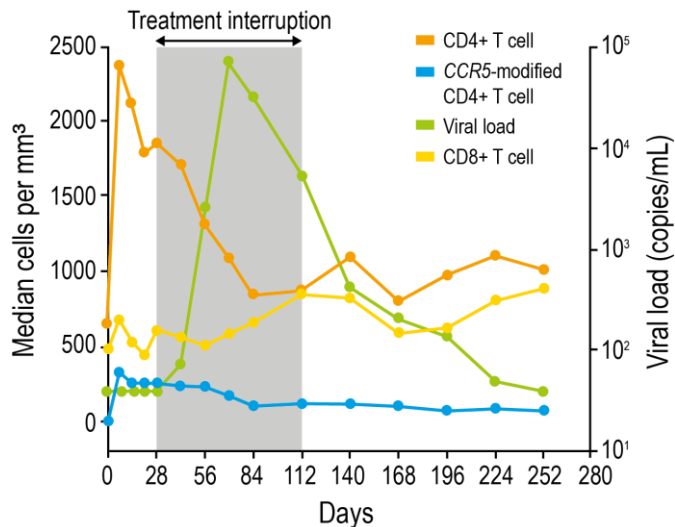


Current research in gene therapy

new vectors, new strategies, new targets

- ZFN editing protects against HIV infection in animal¹ and cellular models²
- Single dose of ZFN-modified autologous CD4+ T cells is feasible in HIV patients on HAART³

VL, median CD4+ T-cell, CD8+ T-cell and CCR5-modified T-cell counts in cohort 1 (n = 6)³



Trials aimed at silencing HIV transcription are ongoing⁴

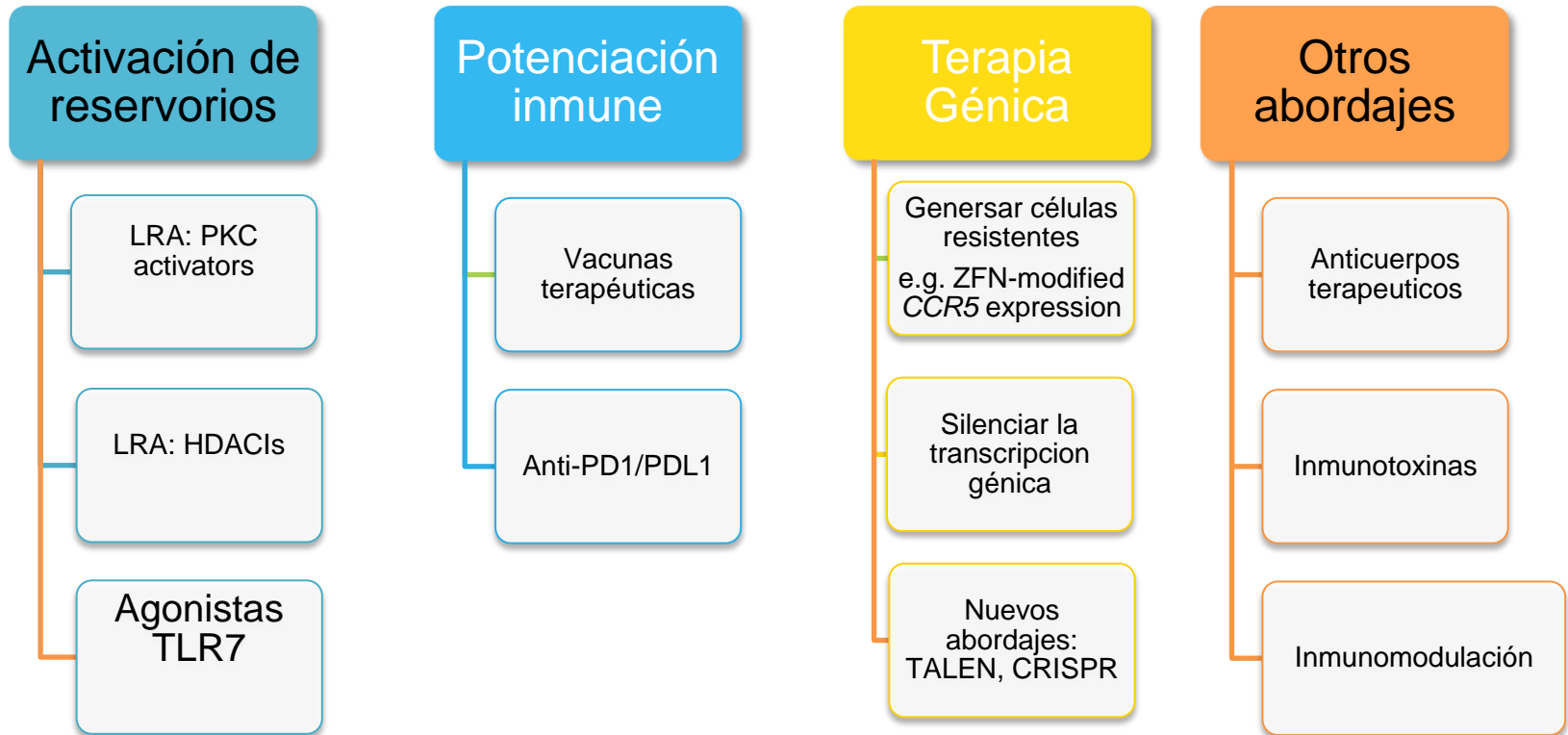
Trial	Intervention(s) • Outcome measures	Status; ECD
NCT01787994 Phase I NR, open-label	MazF endoribonuclease (MazF-T)-modified autologous CD4+ T cells • AEs and antiviral effects	Recruiting; December 2015
NCT01177059 Phase II Observational, long-term follow-up	Anti-HIV-1 ribozyme (OZ1) autologous CD34+ haematopoietic progenitor cells • AEs and reportable events	Active, not recruiting; December 2020
NCT00131560 Phase II Open-label	VRX496-modified autologous T cells • Changes in VL, CD4 count • Safety	Active, not recruiting; June 2023

- New molecular tools to delete HIV-1 proviral DNA are being developed
- RNA-directed gene editing specifically eradicates latent DNA and prevents new HIV-1 infection⁵

AEs, adverse events; ECD, estimated completion date; HAART, highly active antiretroviral therapy; NR, non-randomised.

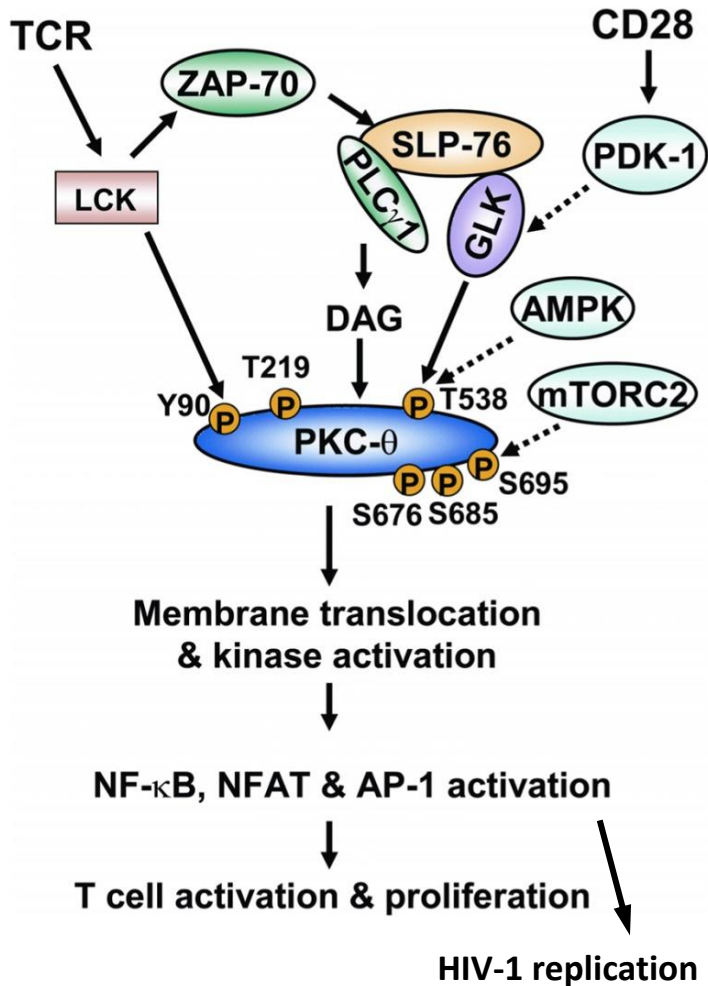
1. Didigu CA, et al. Blood 2014;123:61–9. 2. Badia R, et al. CROI 2014; Poster 171. Available from: <http://www.croiconference.org/sessions/zinc-finger-endonuclease-targeting-ledgfp75-inhibits-hiv-1-integration>. 3. Tebas P, et al. N Engl J Med 2014;370:901–10. 4. ClinicalTrials.gov. Available from: <http://clinicaltrials.gov/ct2/home>. 5. Hu W, et al. Proc Natl Acad Sci USA 2014;111:11461–6. (All URLs accessed June 2015).

Estrategias para disminuir o eliminar los reservorios.

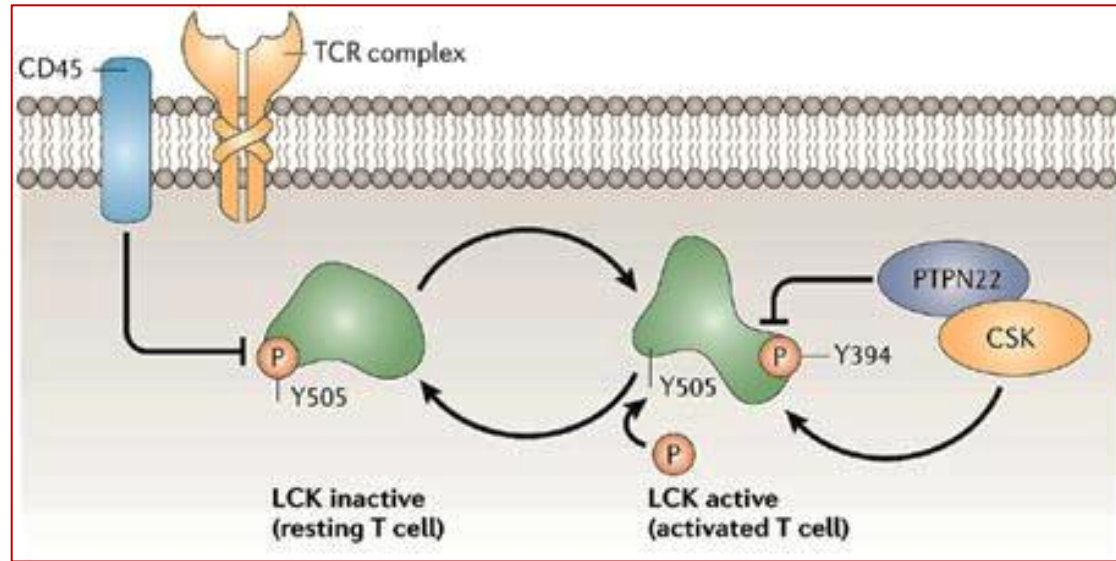


La Tirosin kinase p56Lck participa en la activación de los linfocitos T

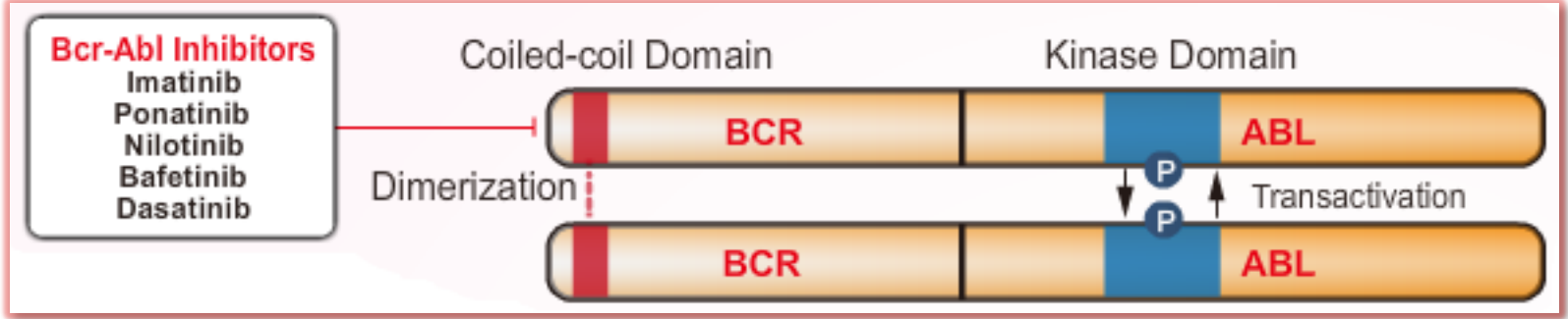
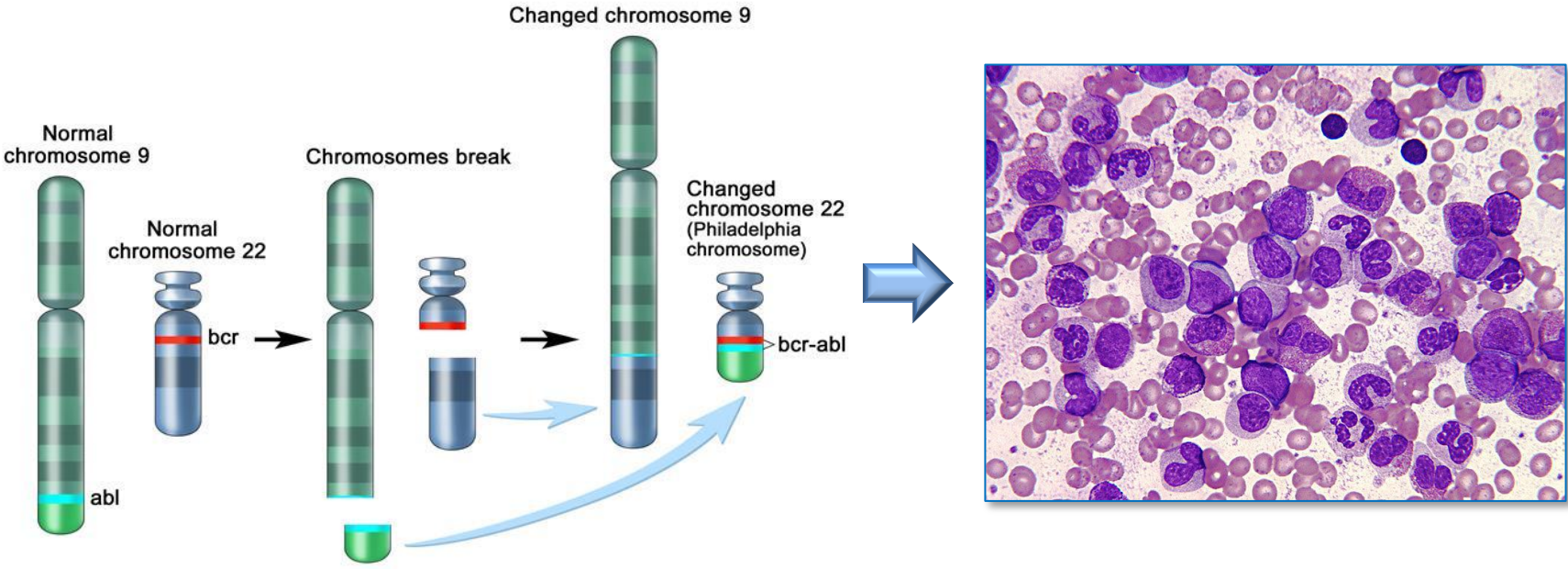
p56Lck is essential for TcR-mediated T-cell activation.



Autophosphorylation of LCK at Y394 is an early event in T-cell activation, leading to phosphorylation of downstream substrates by LCK

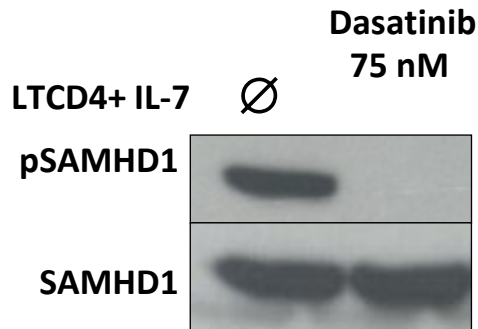


Dasatinib: un inhibidor de tirosin-kinasas utilizado en el tratamiento de la leucemia mieloide crónica

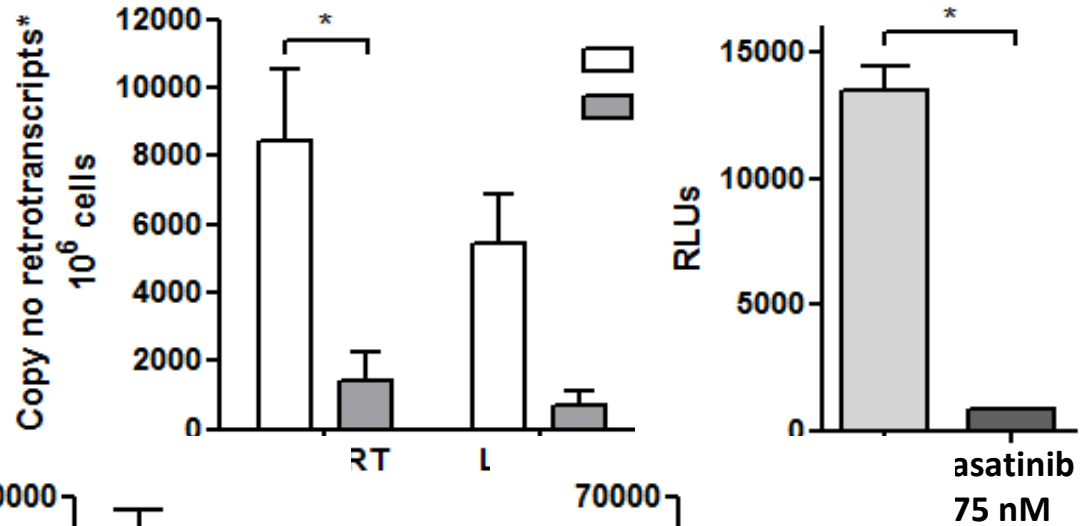


DASATINIB disminuye la infección por VIH-1 “in vitro” mediante un mecanismo antiviral específico: aumenta la actividad de SAMHD1

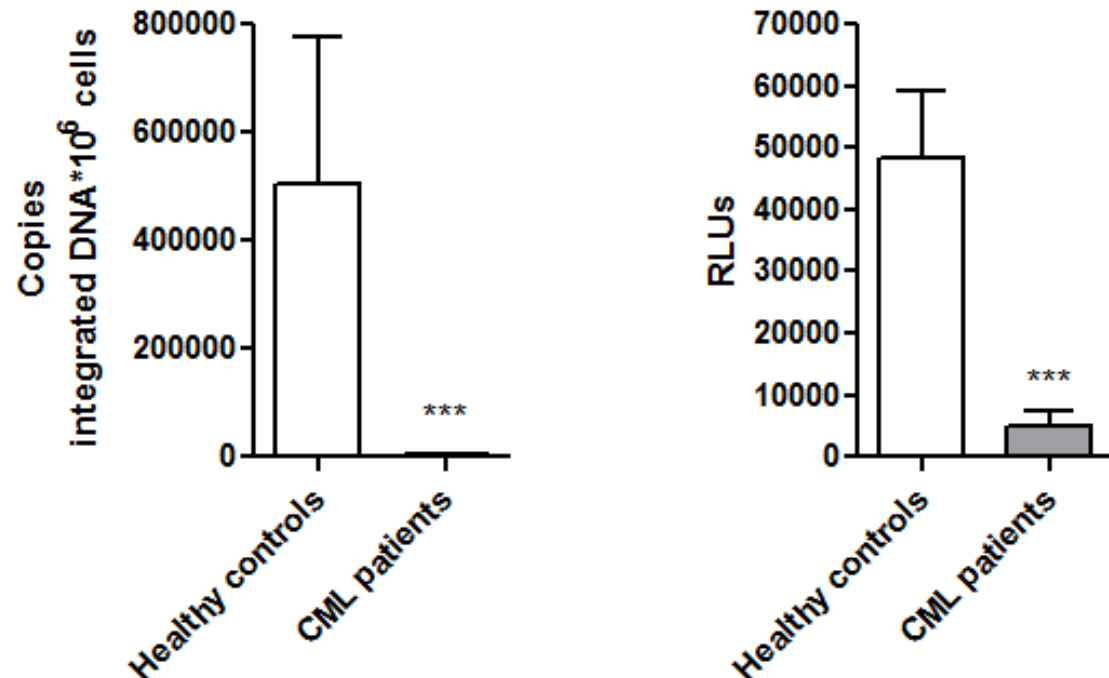
A. Dasatinib bloquea la fosforilación de SAMHD1



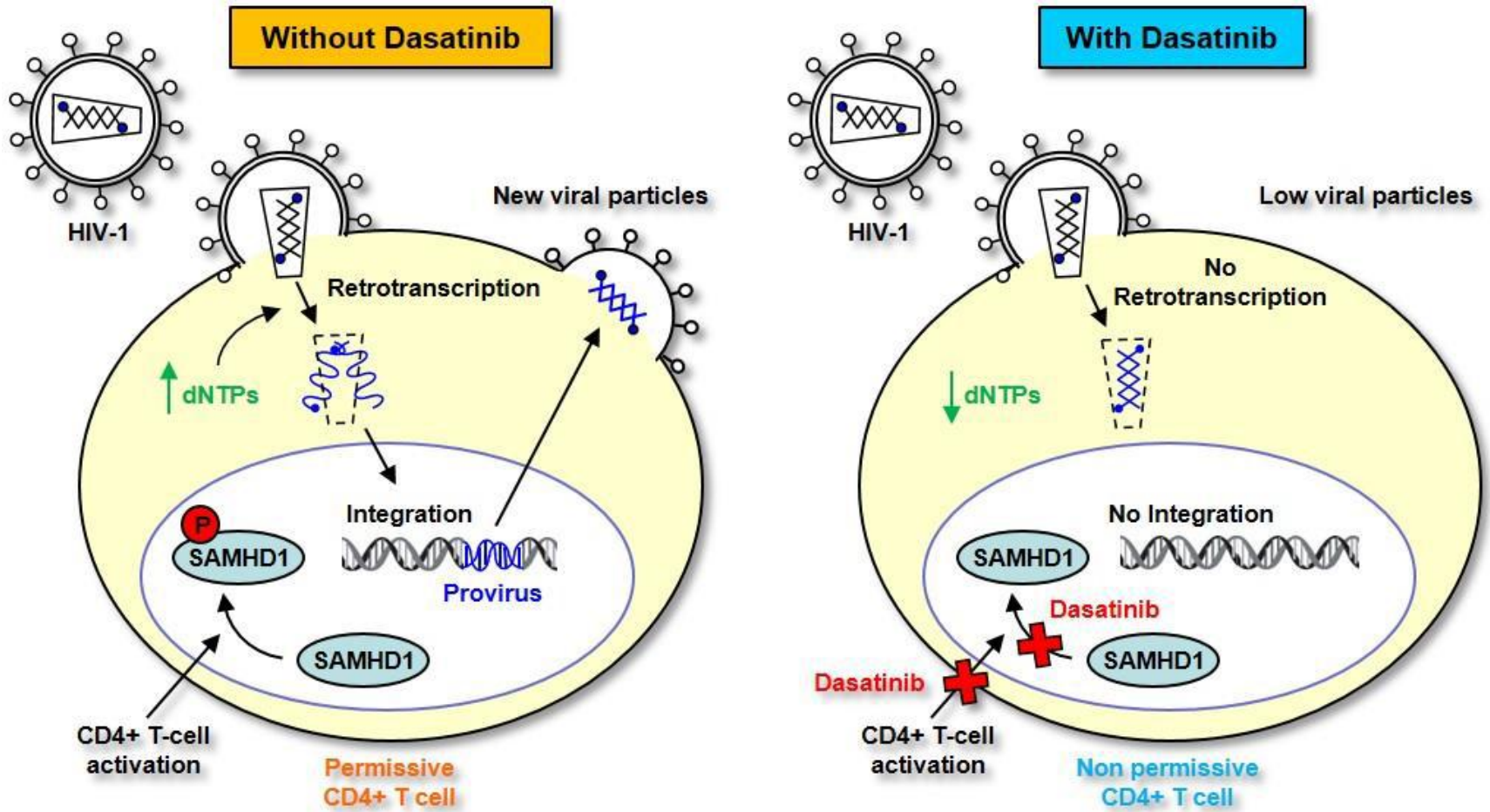
B. Dasatinib inhibe la RT y la replicación viral “in vitro”



C. Los CD4 de pacientes tratados con Dasatinib por LMC son resistentes a la infección por el VIH “ex vivo”



Tratamientos para la curación. TKI en infección aguda



LA CURACIÓN DEL VIH ¿UNA FRONTERA LEJANA?

LA MISMA CELULAS PUEDE ALBERGAR UN VIRUS LATENTE O REPLICARLO

- Necesitamos comprender con mayor profundidad la latencia y la reactivación
- ¿Cómo se mantienen los reservorios?

MUCHOS VIRUS INTEGRADOS SON DEFECTIVOS

- ¿Como identificar las células latentemente infectadas y las que tienen virus competentes para la replicación?
- ¿Cual es el mejor método para monitorizar los reservorios en sus distintos compartimentos? → “La carga viral de los reservorios”
- How to measure the viral reservoir in different compartmentsHow to identify

LA PARADOJA DE LOS FÁRMACOS ANTI-LATENCIA

- Si son demasiado débiles → Falta de impacto sobre el reservorio
- Si son potentes → Potencialmente tóxico (tormento de citocinas)

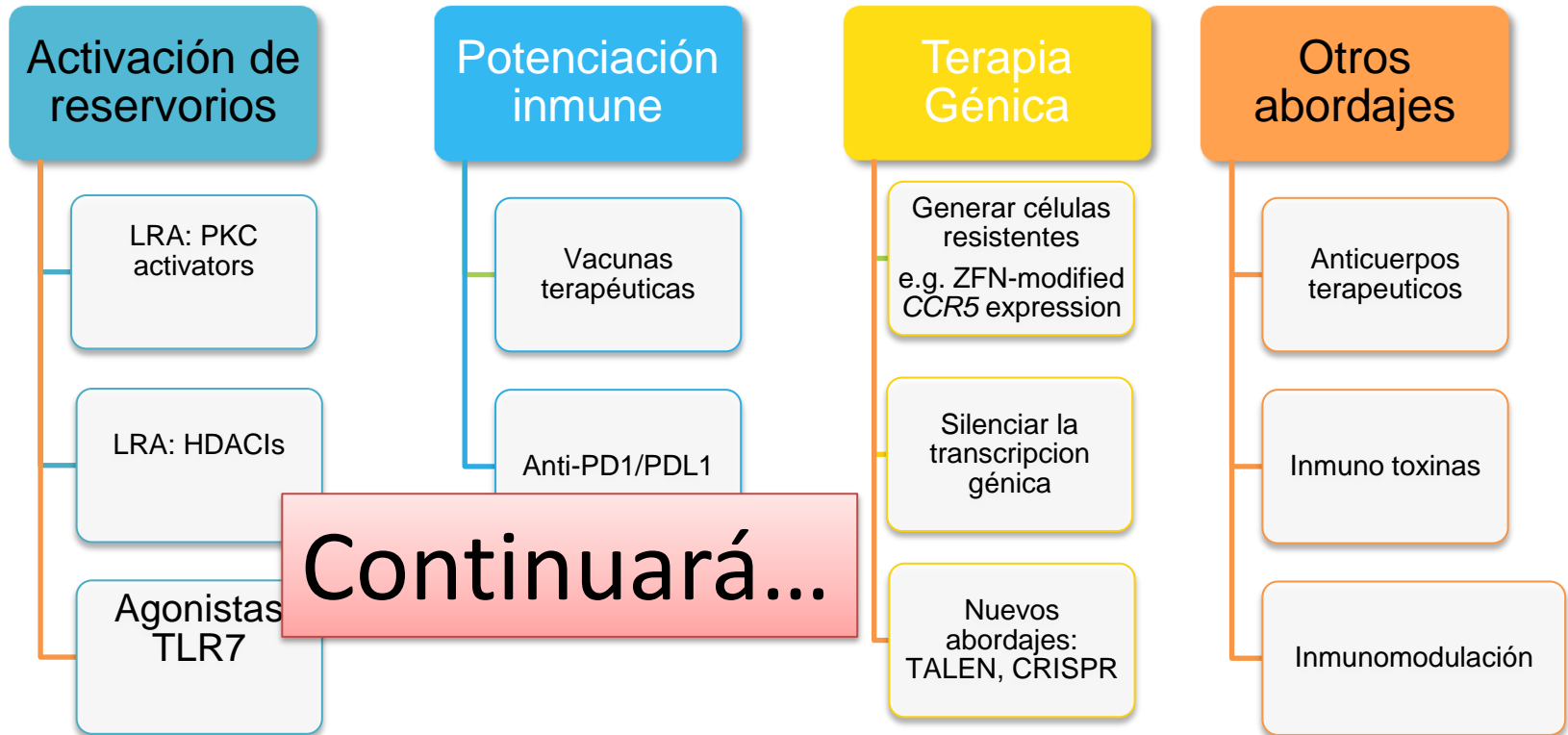
RIESGO DE EFECTOS GRAVES

- Fármacos con baja especificidad de diana

EL VIRUS MANTIENE LA MEMORIA, EL SISTEMA INMUNE SE OLVIDA

- ¿Cómo recuperar la memoria y la actividad antiviral del sistema inmune?

Estrategias para disminuir o eliminar los reservorios.



- Prototipos actuales han tenido poco éxito
- Algunos son difíciles de llevar a la práctica
- Nuevos abordajes en desarrollo pueden hacer cambiar el escenario