Jornadas Nacionales del Centenario de la Sociedad Argentina de Pediatría – Infectología Pediátrica, 2011

Resistencia a drogas ARV

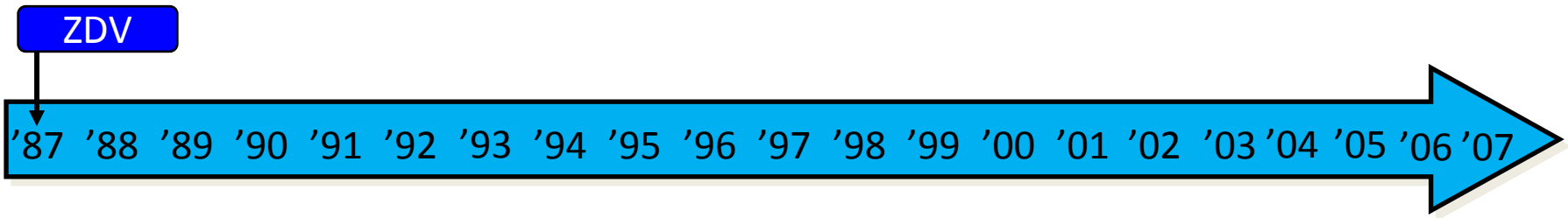
Pedro Cahn

HOSPITAL FERNANDEZ HF

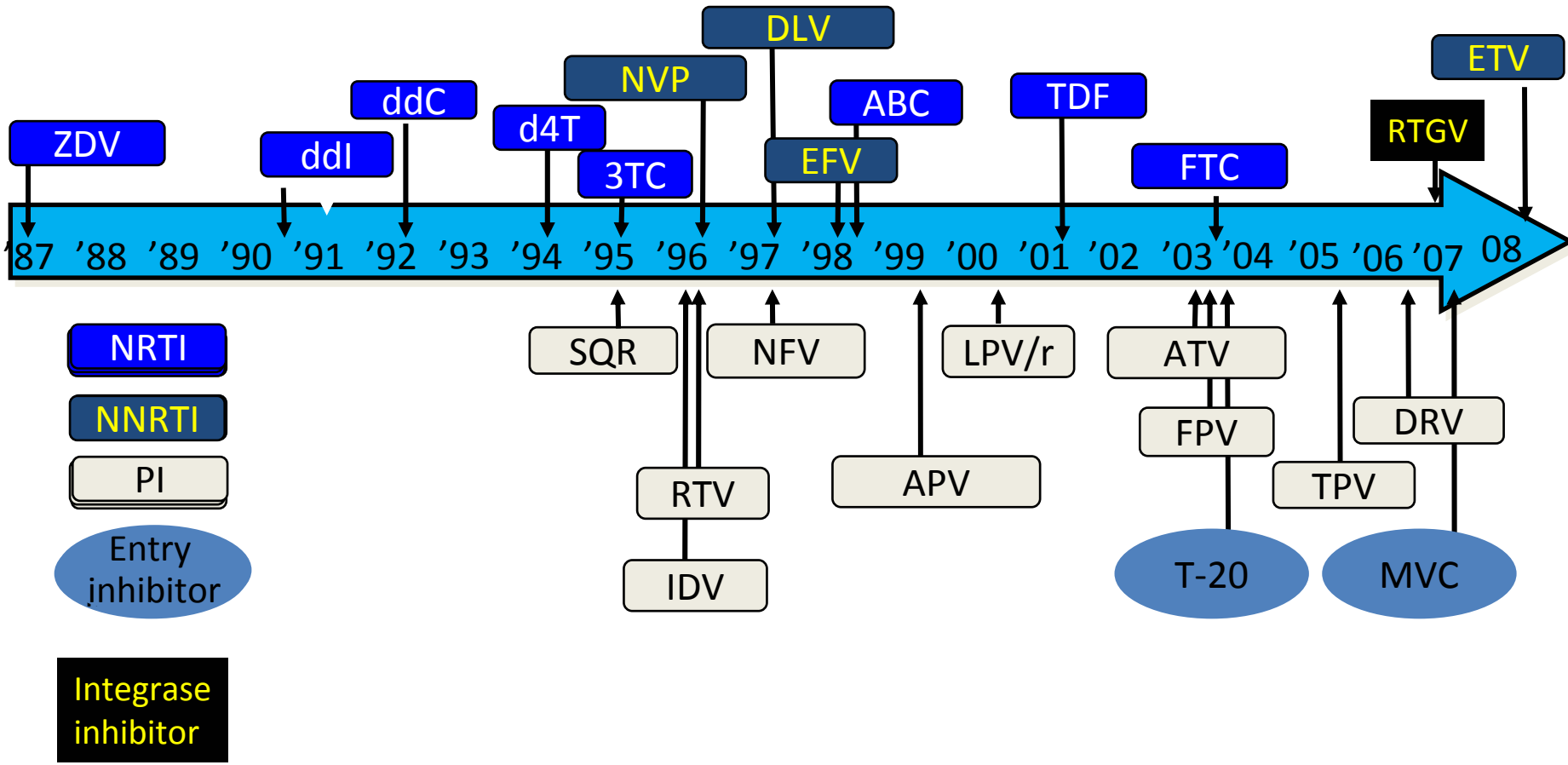
International AIDS Society
Stronger Together

FUNDACION HUESPED
en acción contra el sida

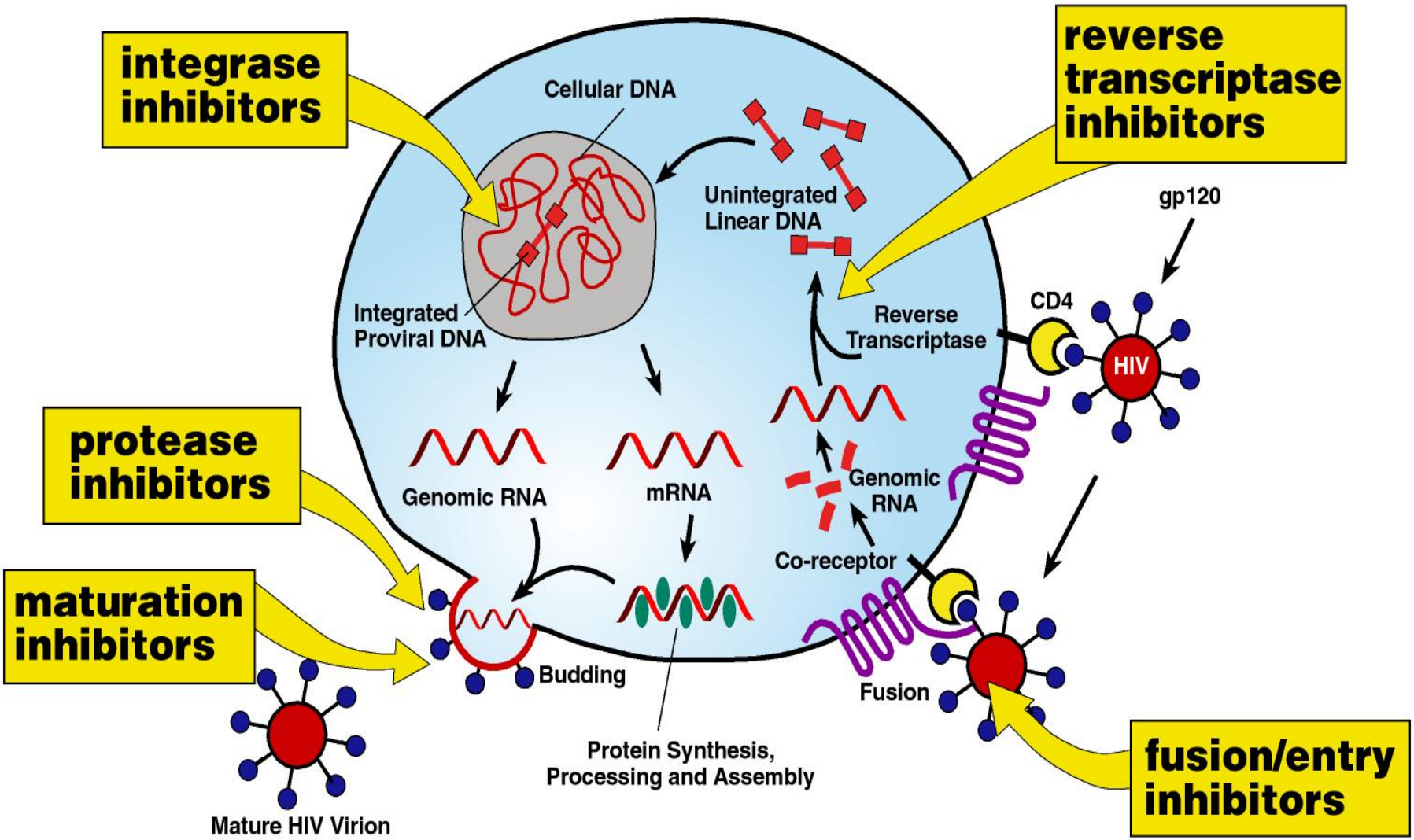
Así comenzó la historia



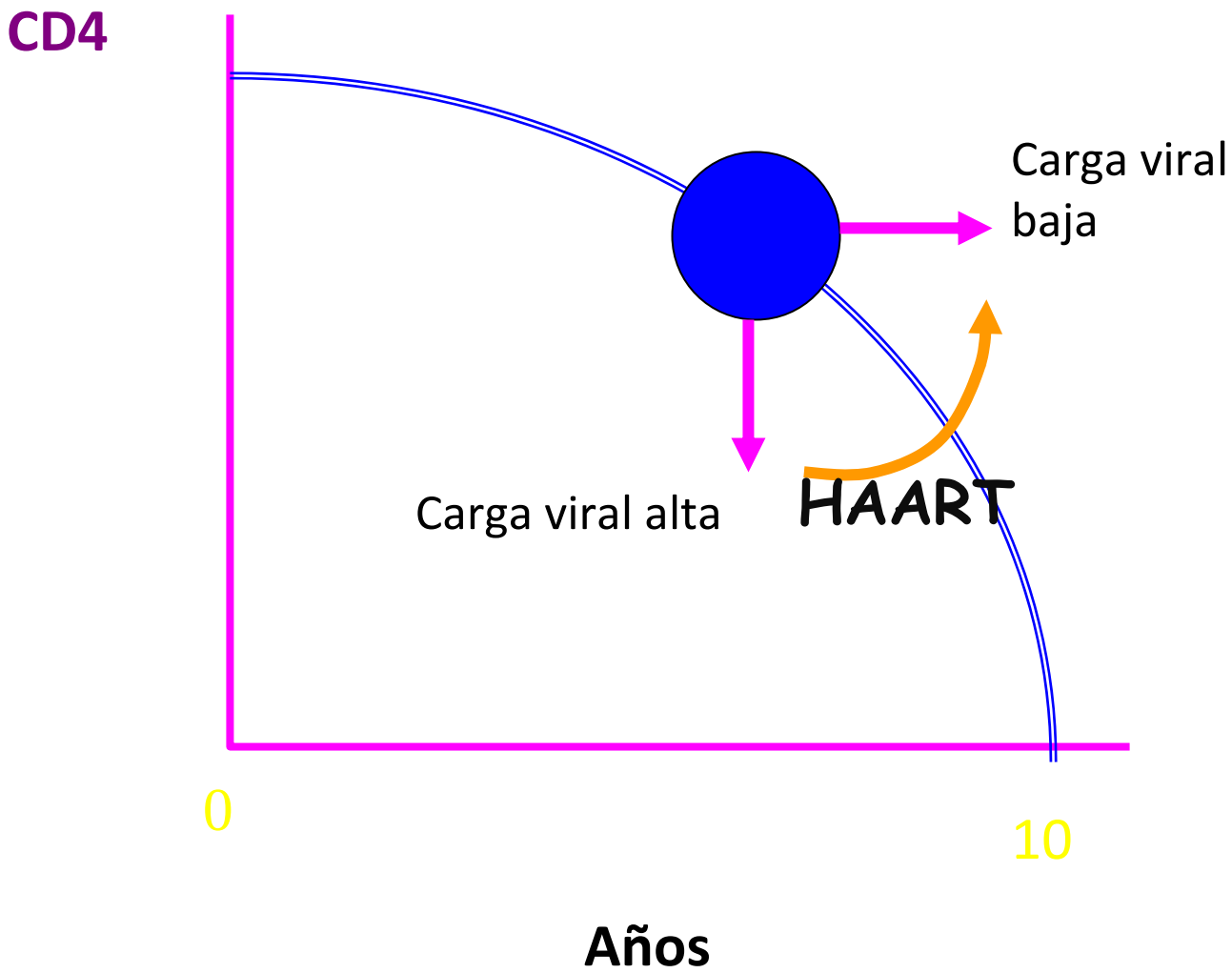
Desarrollo de 25 ARV en el tiempo



HIV Replication Cycle: Targets for Antiretroviral Therapy



HIV:Historia natural



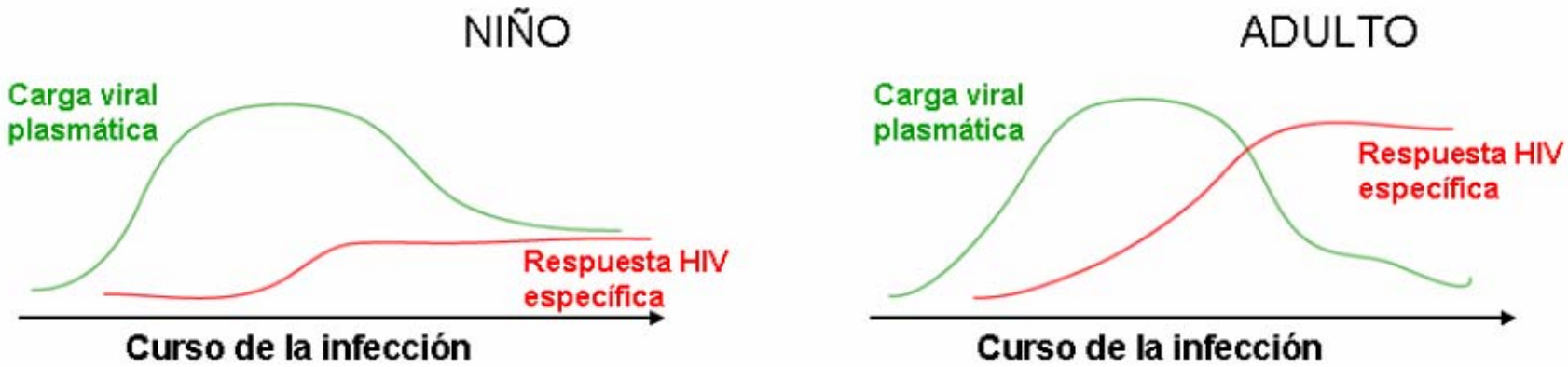
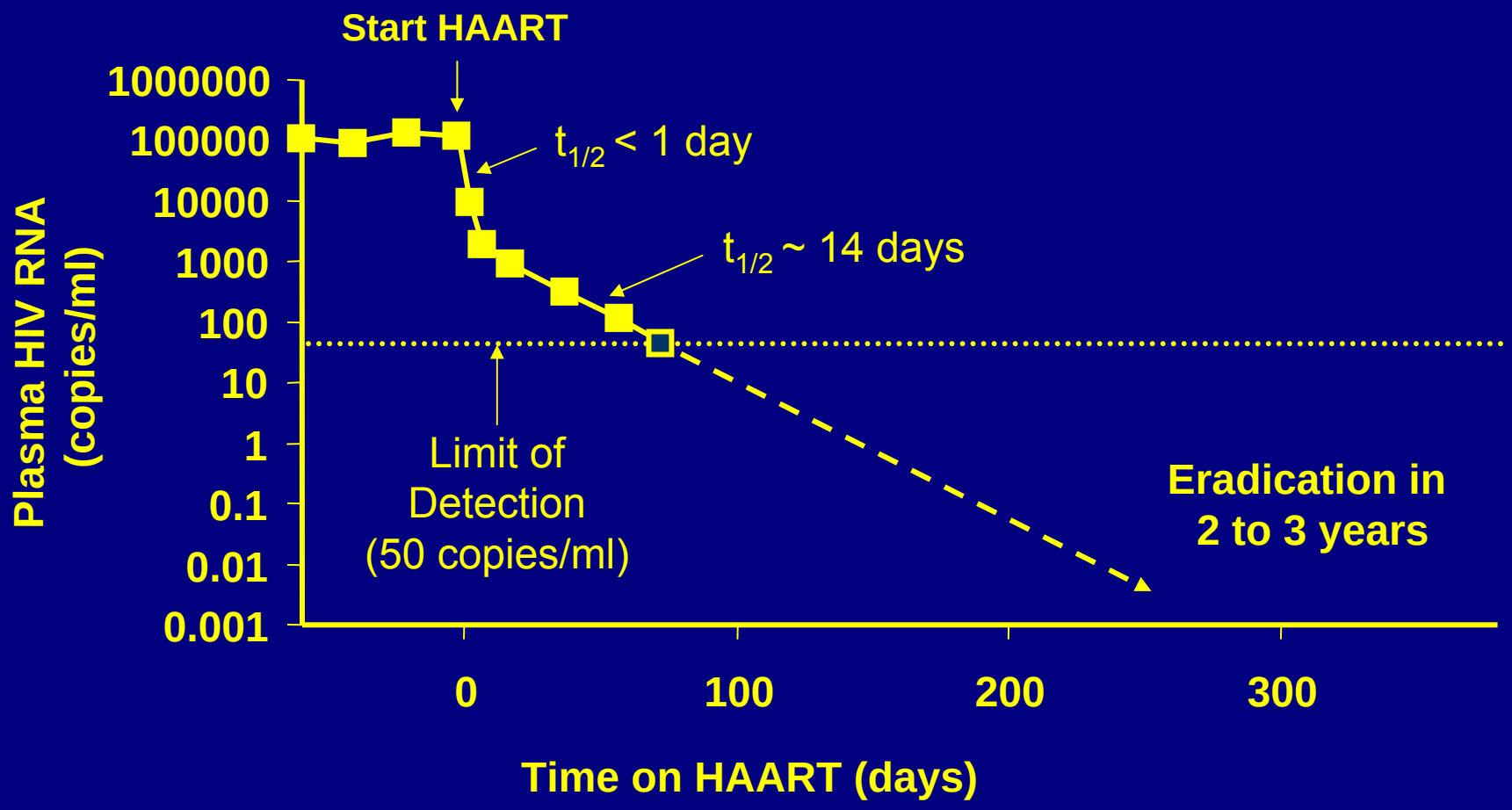


Figura 6: Diferencias en el curso de la carga viral y la respuesta inmune específica entre niños y adultos.

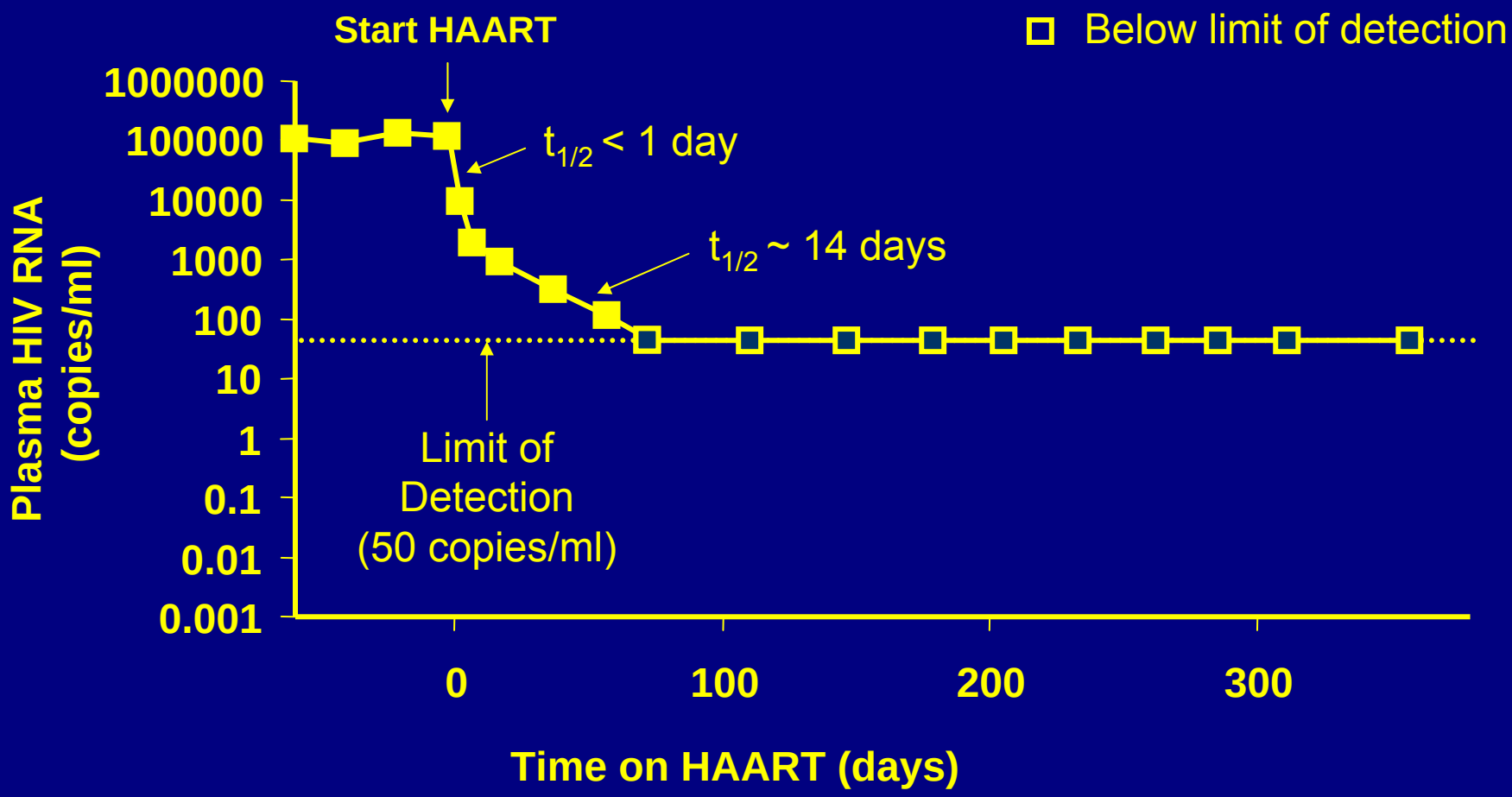
Fuente: Modificado de HIV Medicine 2007 [57].

Dinamica Viral en pts en HAART



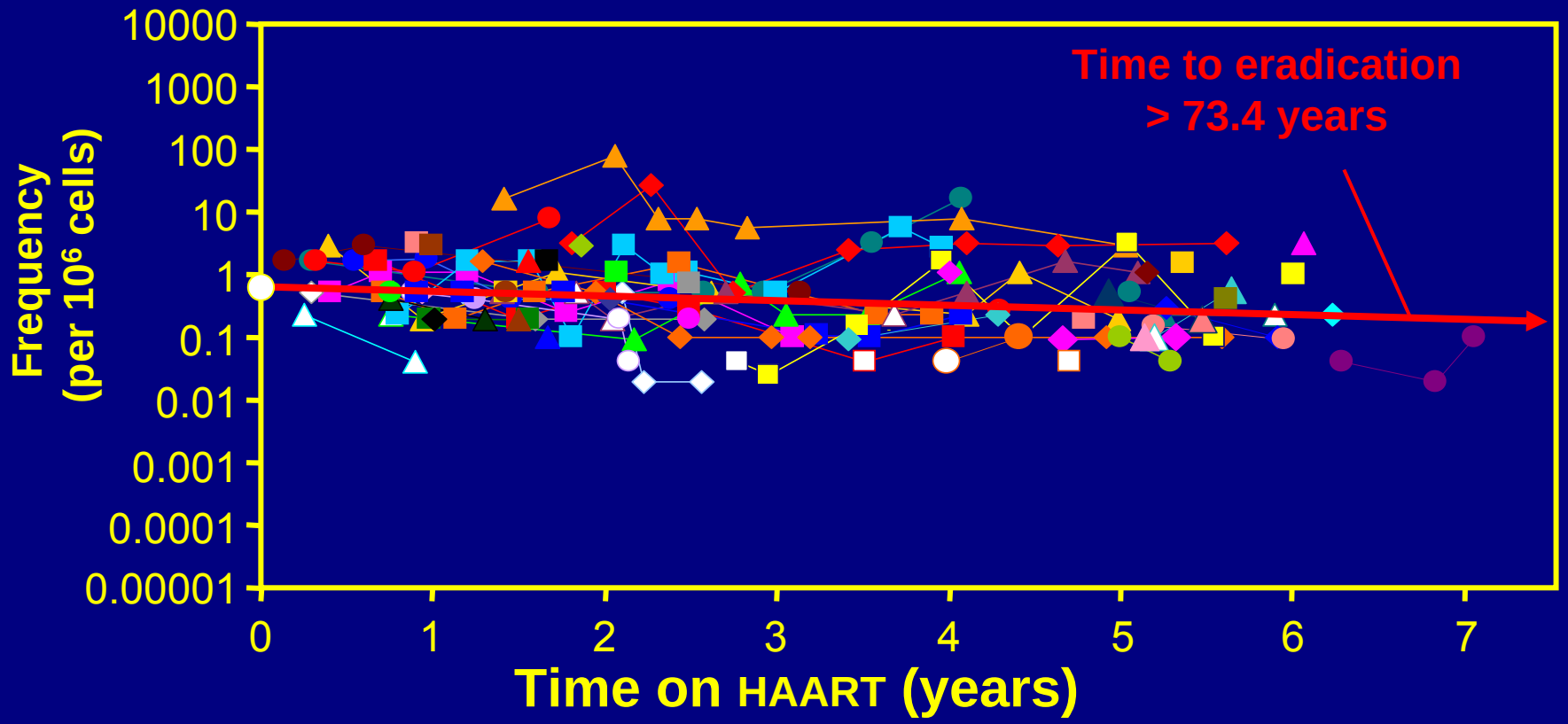
Silicano R: IAC Mexico 2008

Viral dynamics in pts on HAART



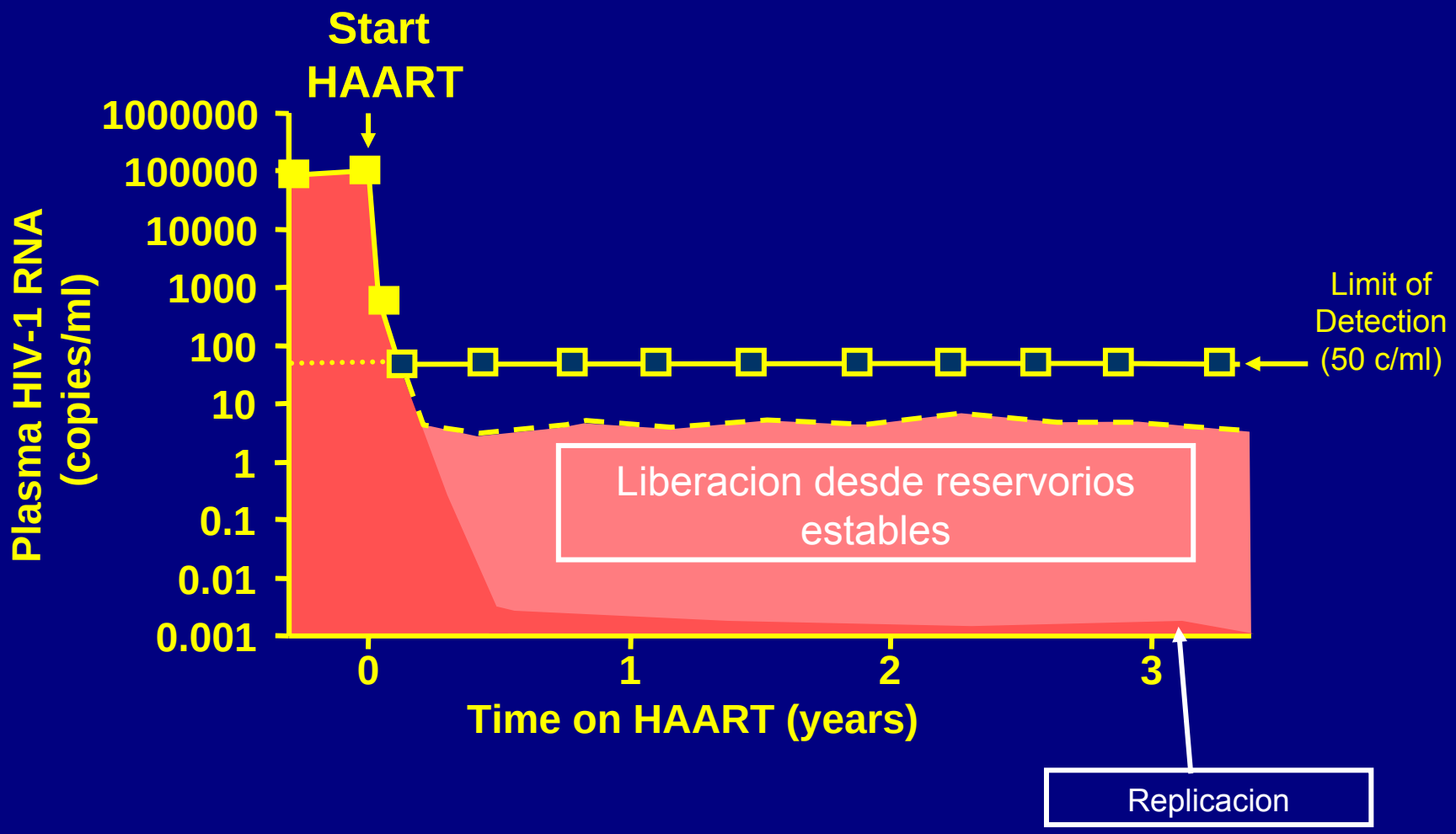
Silicano R: IAC Mexico 2008

Slow decay of latently infected CD4+ T cells



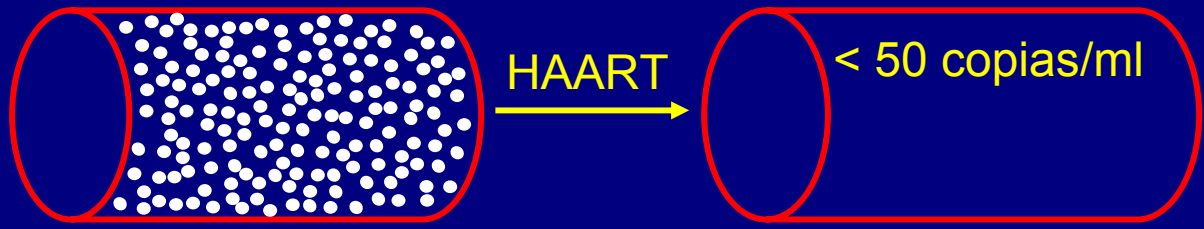
Finzi et al., Science, 1997
Wong et al. Science, 1997
Chun et al., PNAS, 1997
Chun et al., Nature Med., 1995

Viremia Residual Durante HAART

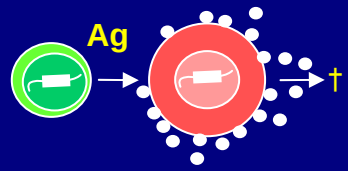


Silicano R: IAC Mexico 2008

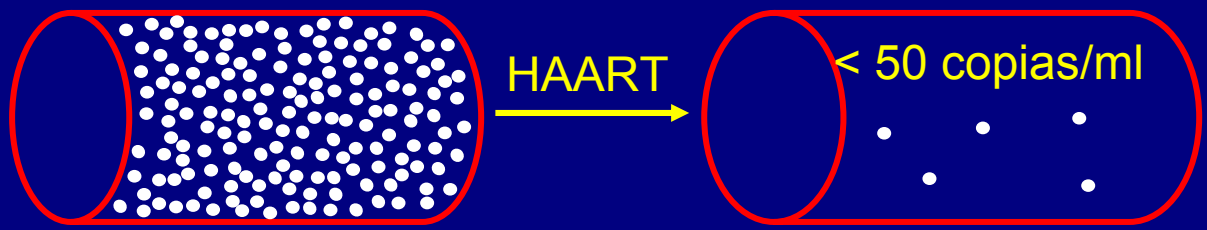
- **HAART reduce viremia < 50 copias/ml**



- **HIV persiste en las celulas T de los reservorios**

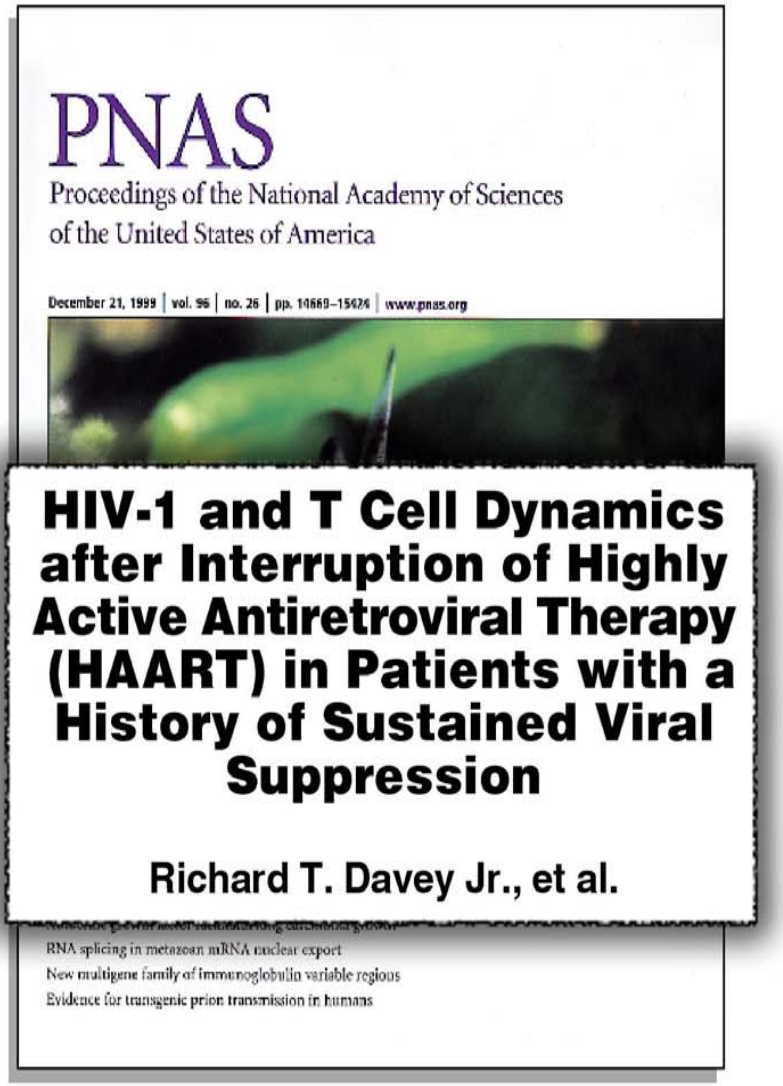


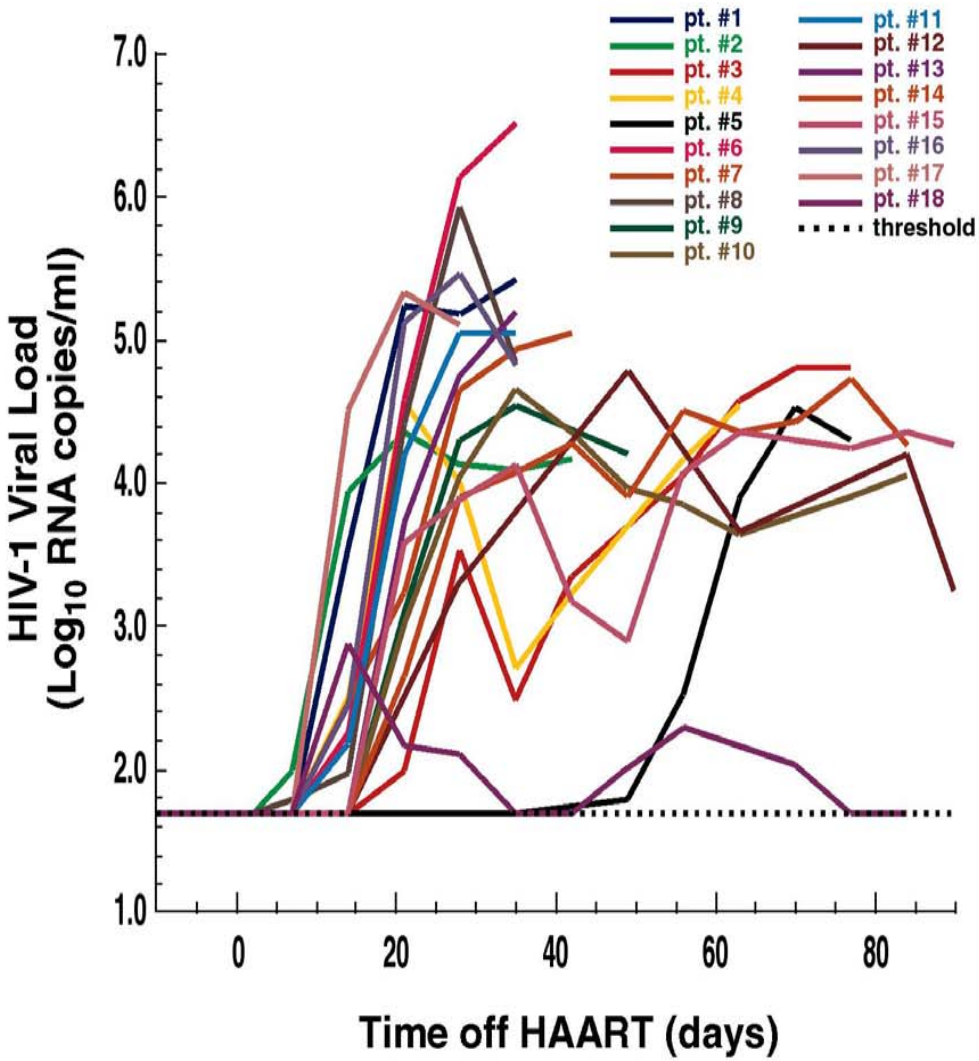
- **Pacientes en HAART tienen <u>viremia residual</u>**



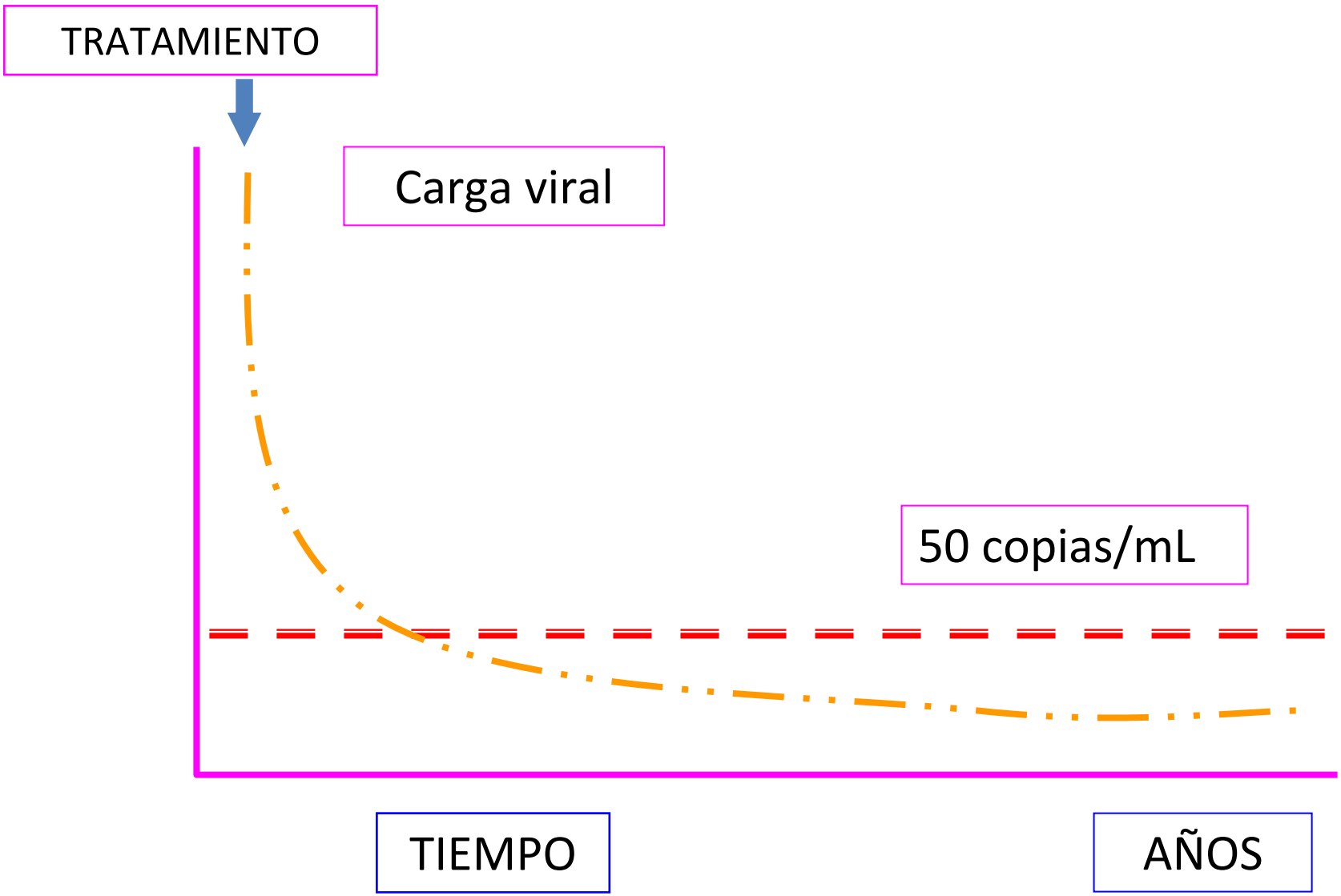
Dornadula et al., JAMA, 1999
Palmer et al., PNAS, 2008

Rebound of HIV Following Discontinuation of Therapy

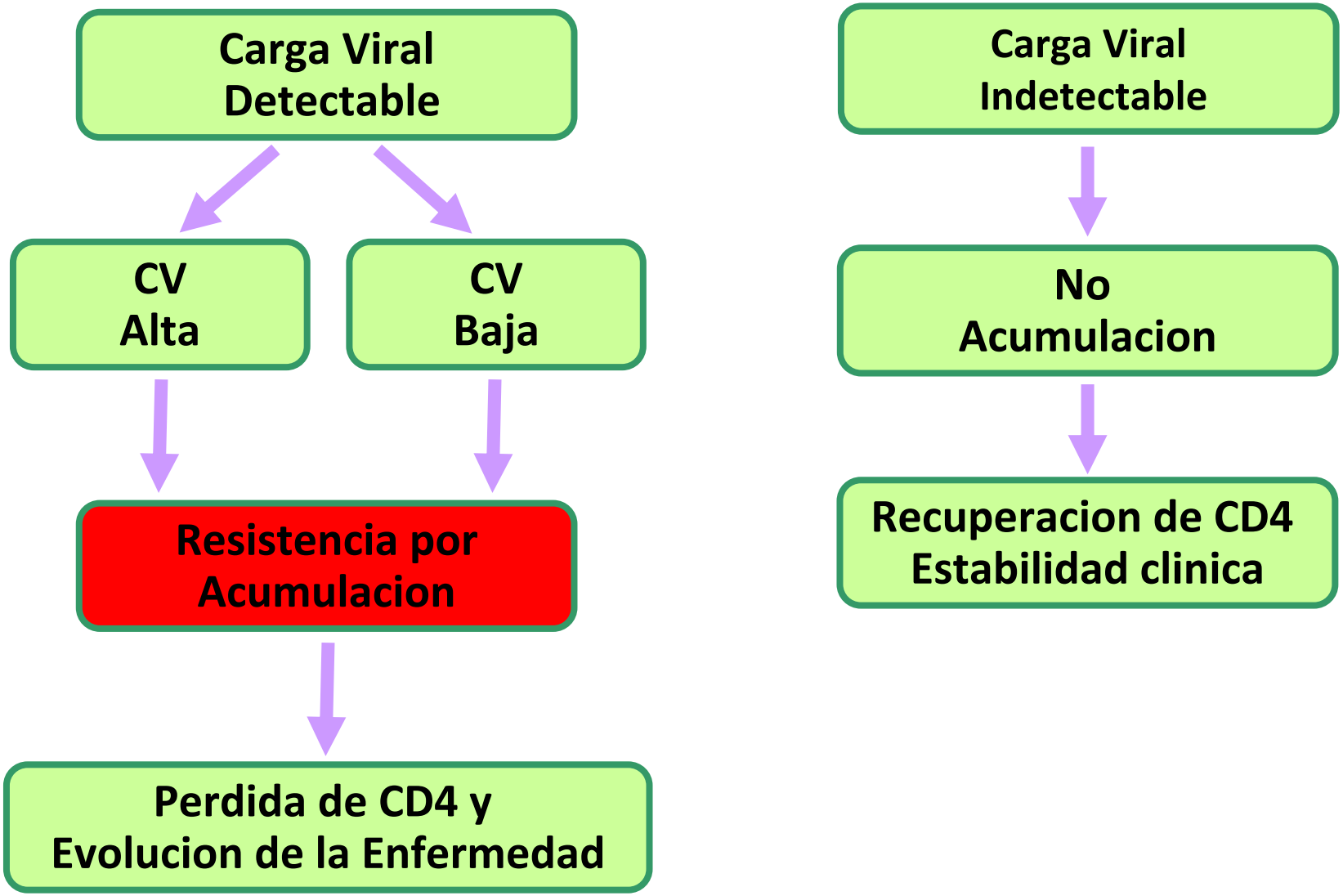




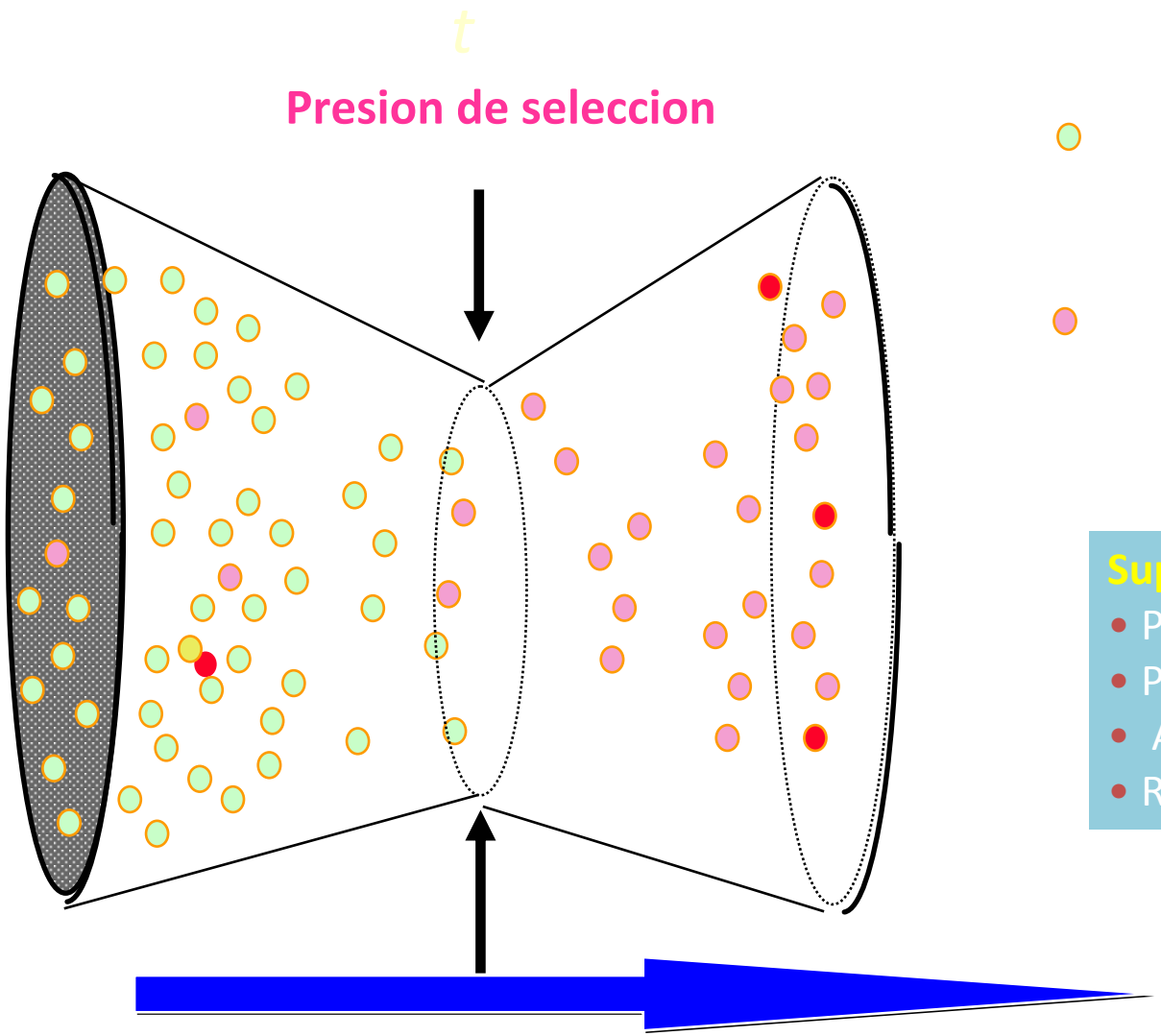
OBJETIVOS DE LA TERAPIA ARV



Viremia y Evolucion de Enfermedad



Dinamica viral y resistencia a los ARV



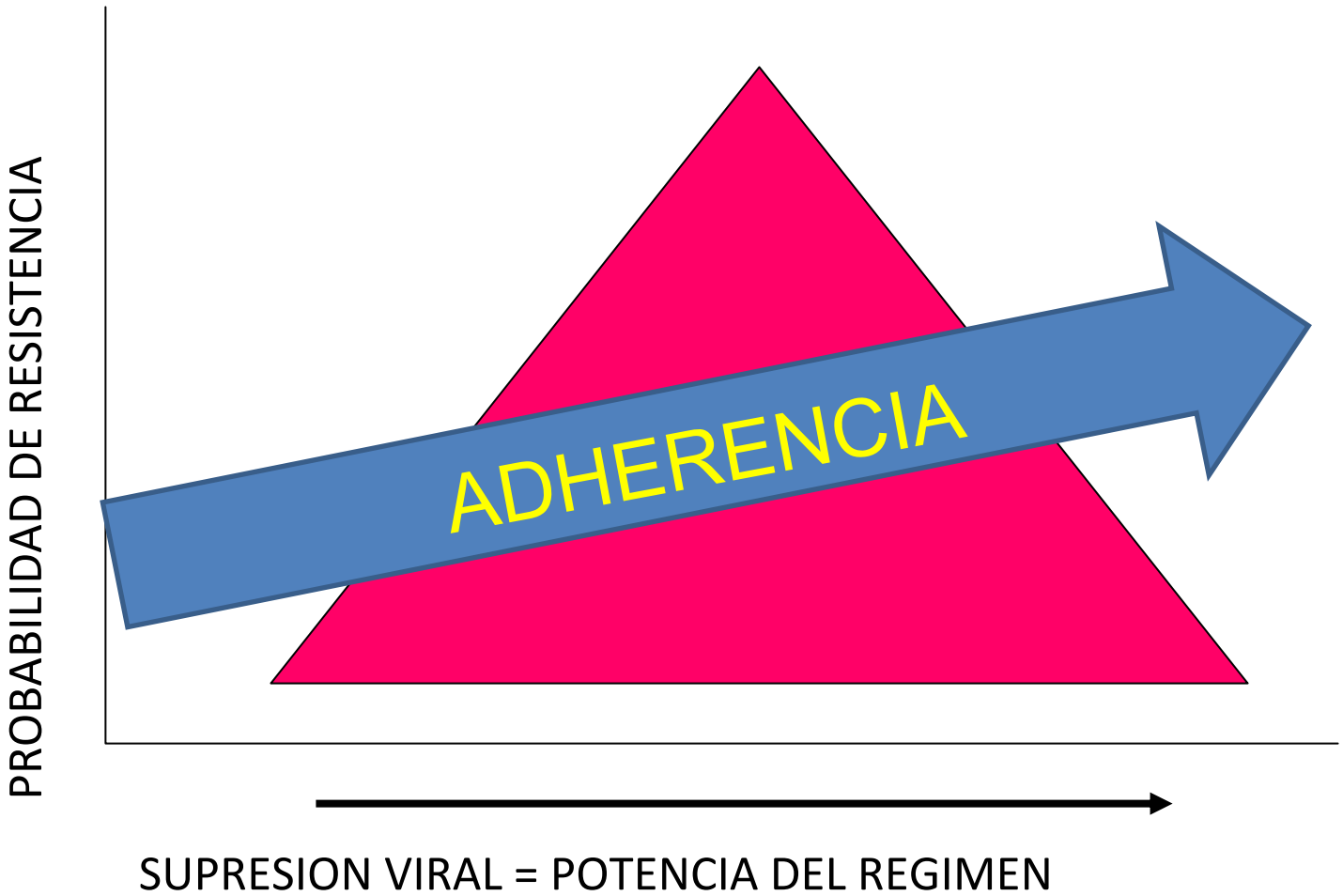
“cepa salvaje” (susceptible)

“virus mutante” (resistente)

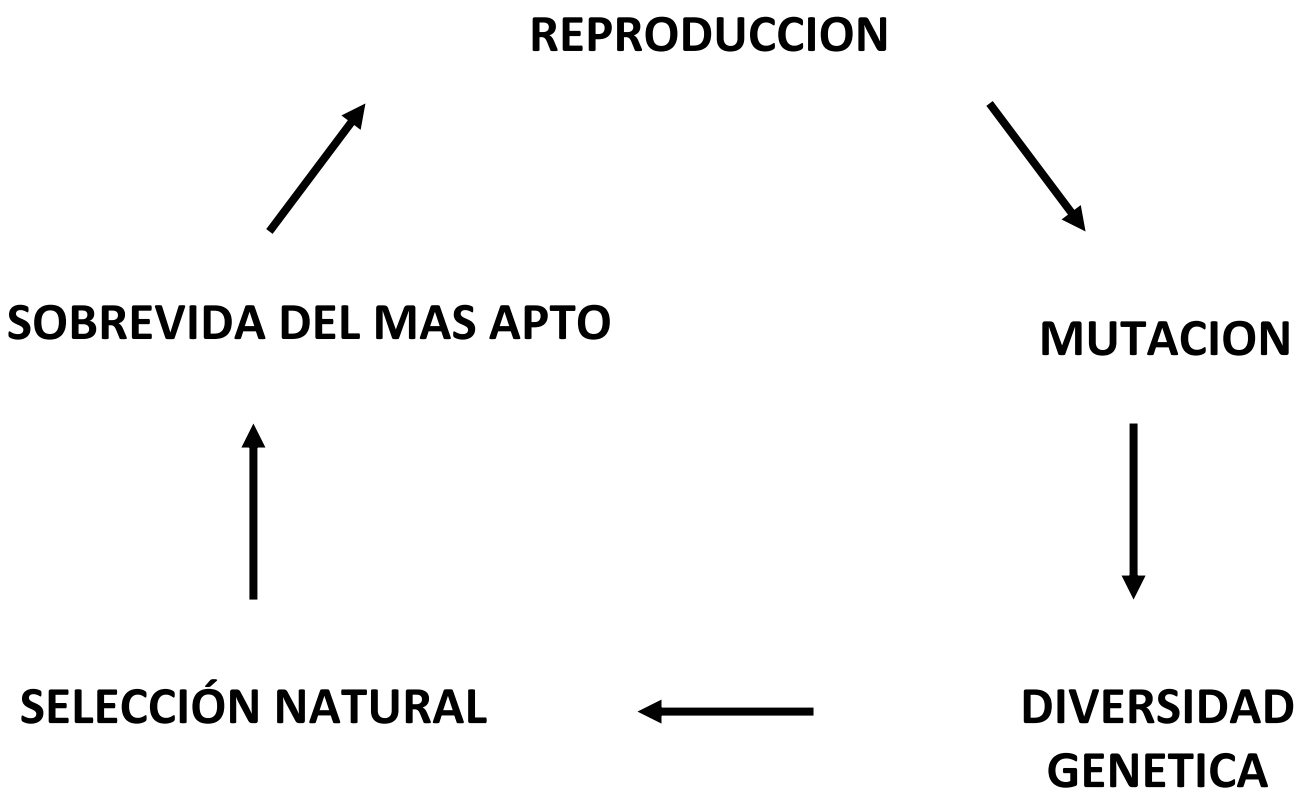
Supresión Incompleta

- Potencia
- PK
- Adherencia
- Resistencia 1ª

Resistencia vs. supresión viral



Evolucion Darwiniana



E Emini, 1996

Fallo virologico

- Fallo en reducir la carga viral un logaritmo a las cuatro semanas de iniciado un nuevo Tx.
- Fallo en alcanzar una máxima supresión de la carga viral a < 400 copias a 24 semanas y/o <50 copias a las 48 semanas Tx.
- Cualquier nivel de carga viral detectable luego de dos mediciones <50 copias confirmado en dos veces consecutivas.

Which patients have triple-class resistance?

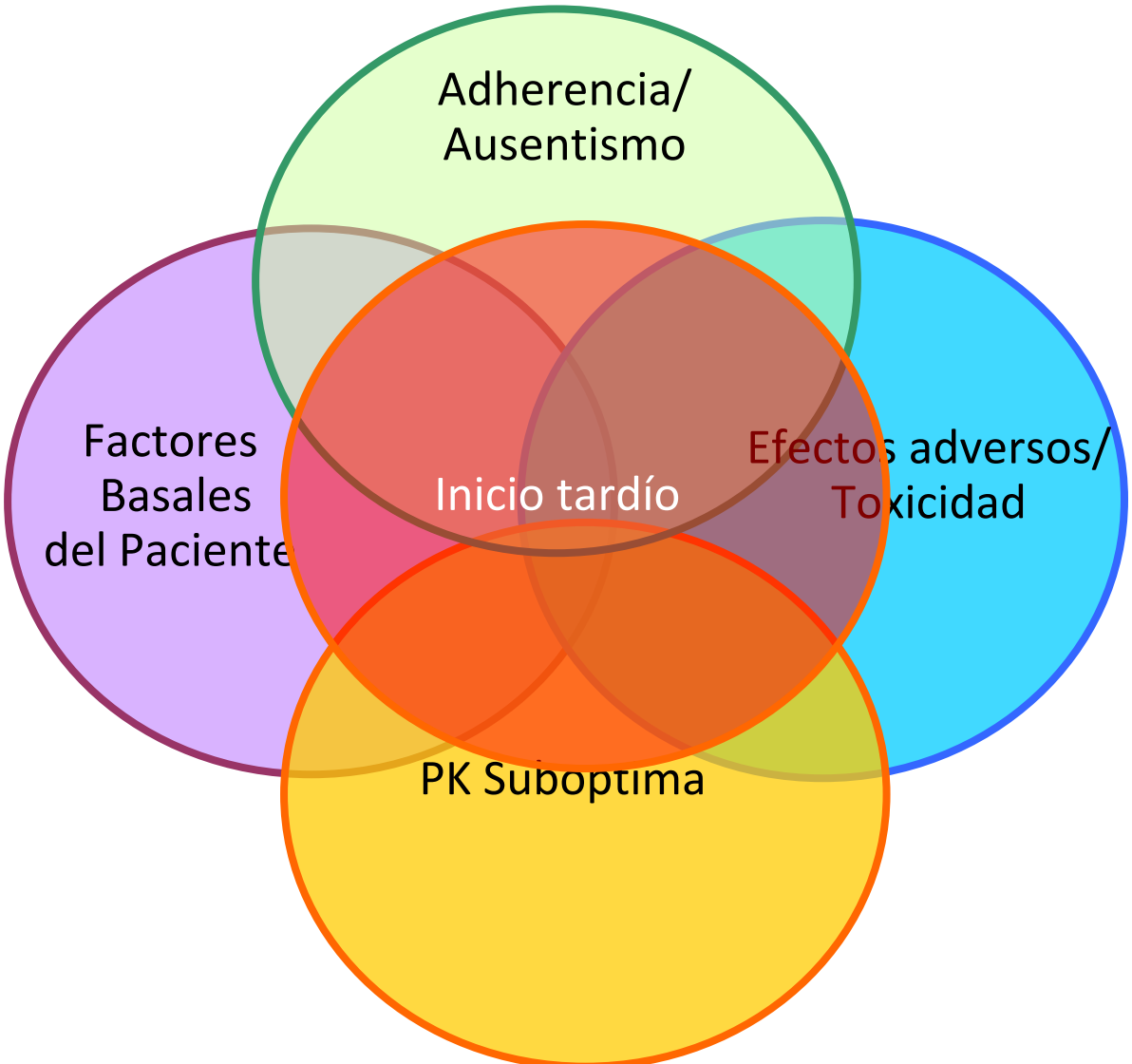
- University of North Carolina HIV Cohort Study
  - Chart review: 121 (8%) of 1466 triple-class resistance
- Independent predictors of triple class resistance (OR: 95% CI)
  - **Prior ARVs (1.7: 1.6, 1.9)**
  - **Non-HAART first regimen (1.7: 1.0, 2.9)**
- Of HAART initiators with triple class resistance (*n*=24):
  - **21 of 24 started unboosted PI (15 with NFV)**
- Results suggest that in era of boosted PIs as initial PI therapy, triple-class resistance will become less common

Baseline characteristics

Patient characteristics	Triple-class resistance		*p*-value
	NO	YES	
Total, *n* (%)	1466 (92)	121 (8)	
Nadir CD4+ cell count (cells/mm^3), median (IQR)	144 (34, 305)	46 (12, 134)	<0.001
Peak HIV RNA level ($\log_{10}$ c/mL), median (IQR)	5.0 (4.3, 5.5)	5.3 (5.0, 5.7)	<0.001
AIDS defining condition, *n* (%)	542 (37)	77 (64)	<0.001
HAART at initiation, *n* (%)	765 (52)	24 (20)	<0.001
Prior NRTI, NNRTI and PI exposure	633 (43)	119 (98)	<0.001

Napravnik S, *et al. XV IHDRW*, Sitges 2006, #78

Factores Contribuyentes al Fallo



Bases moleculares y bioquímicas de la resistencia a las drogas antirretrovirales

Generación de variantes debido a:

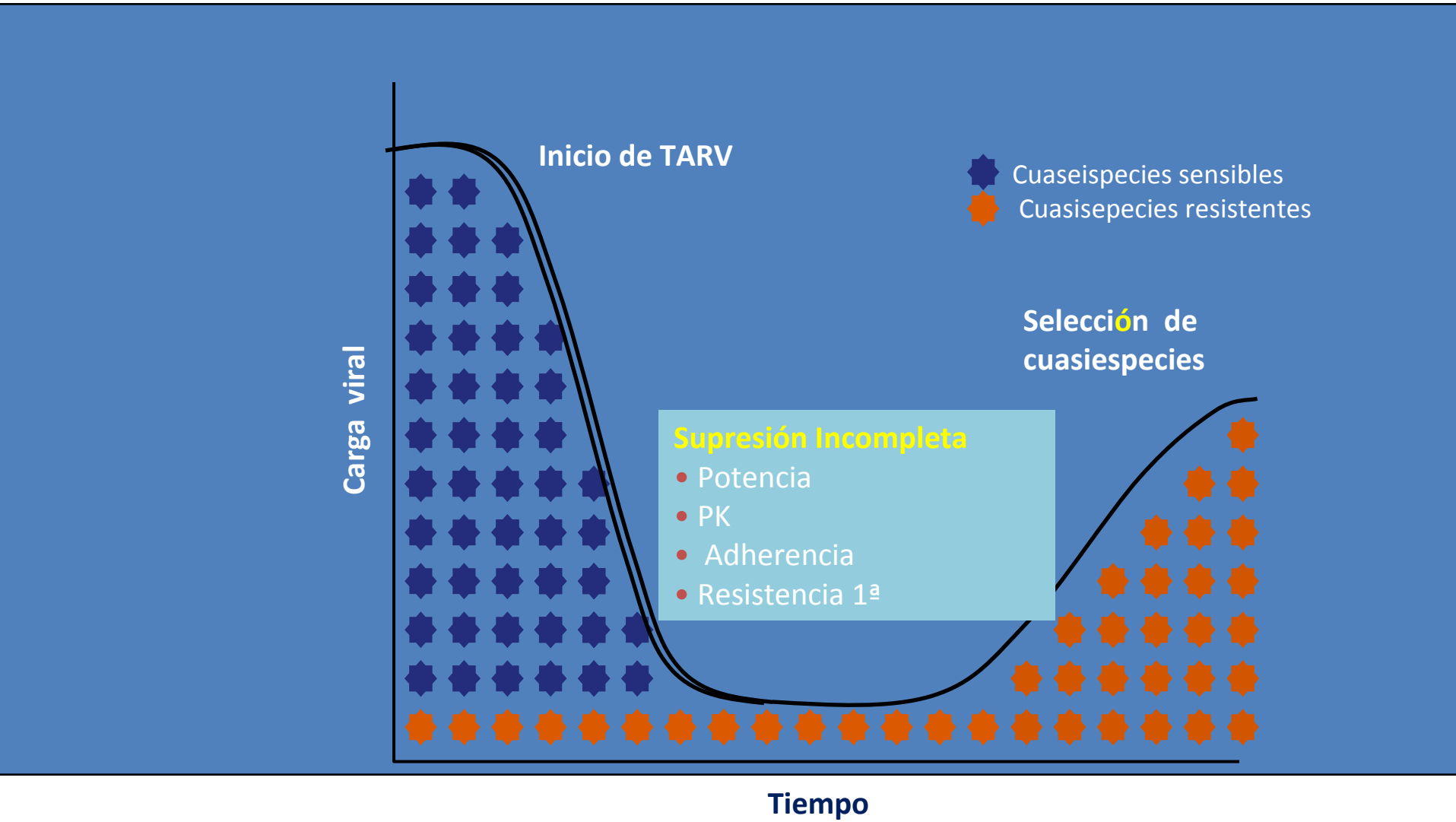
- **la alta tasa de replicación del virus**
- **la alta tasa de error de la TR (**10^{-4} errores/base/ciclo)

1 mutación/10000 bases copiadas = 1 mutación por genoma copiado (HIV = 9.2 kb)

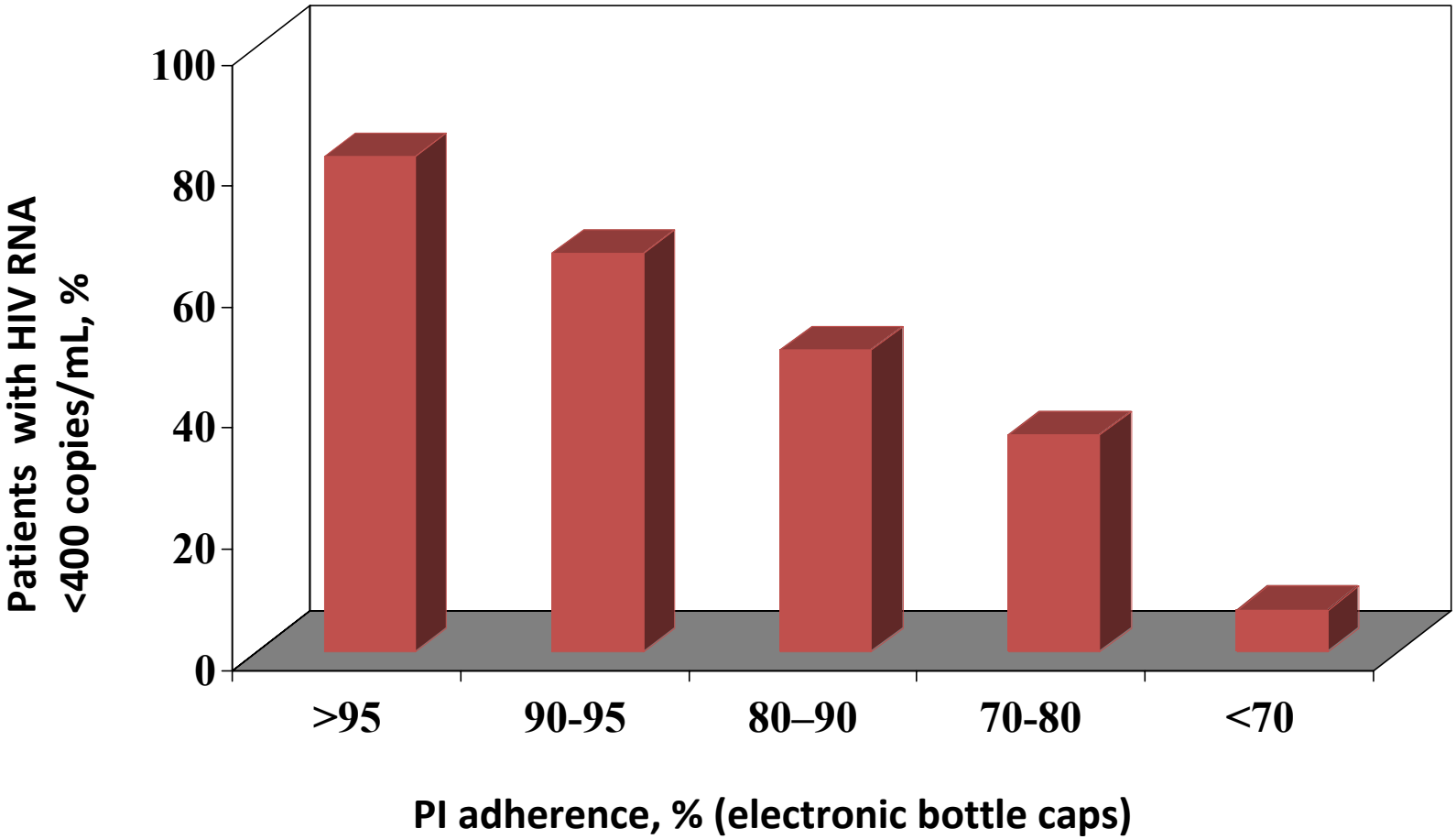
Evolucionan a partir del inóculo viral inicial

Cuasiespecies

Presion de seleccion de los antiretrovirales



Virologic Control falls sharply with diminished adherence

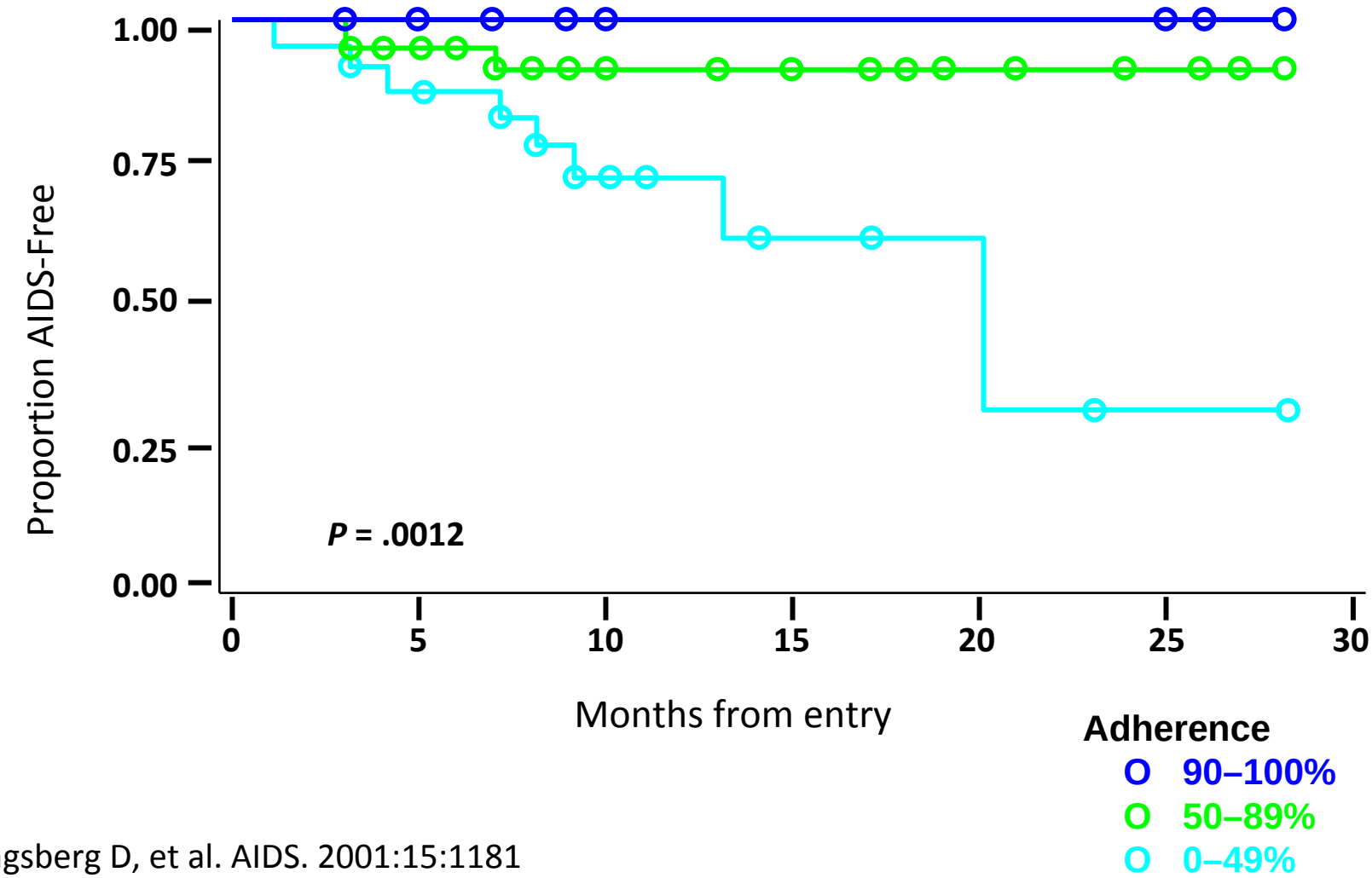


Paterson, *et al.* 6th Conference on Retroviruses and Opportunistic Infections; 1999; Chicago, IL. Abstract 92.

CBB/2002

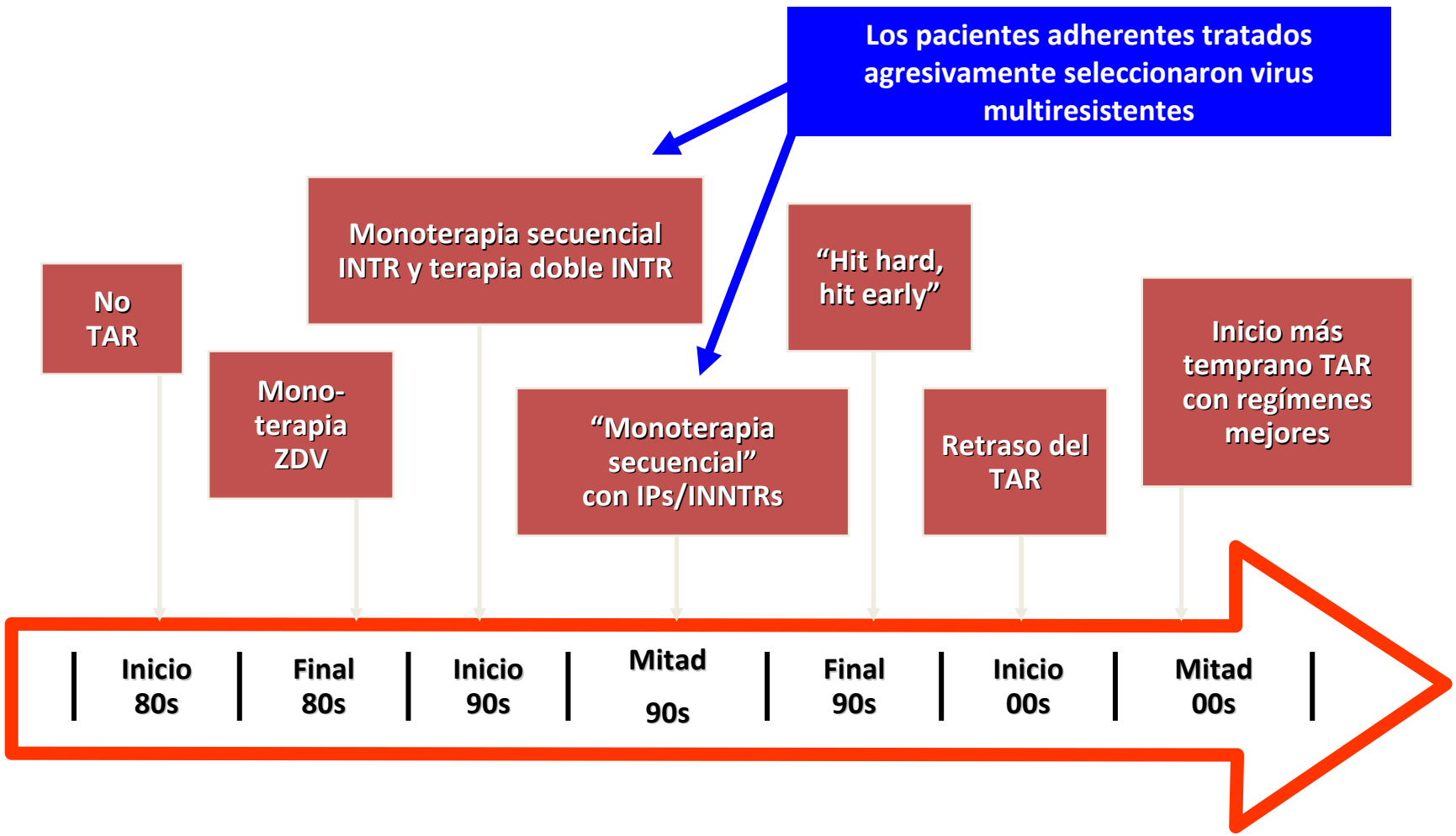
Adherence and AIDS-Free Survival

10% Adherence difference = 21% reduction in risk of AIDS



Bangsberg D, et al. AIDS. 2001:15:1181

Terapia secuencial



Initiation of Antiretroviral Treatment in Women After Delivery Can Induce Multiclass Drug Resistance in Breastfeeding HIV-Infected Infants

Background. The World Health Organization currently recommends initiation of highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV)–infected lactating women with CD4+ cell counts <350 cells/μL or stage 3 or 4 disease. We analyzed antiretroviral drug resistance in HIV-infected infants in the Post Exposure Prophylaxis of Infants trial whose mothers initiated HAART postpartum (with a regimen of nevirapine [NVP], stavudine, and lamivudine). Infants in the trial received single-dose NVP and a week of zidovudine (ZDV) at birth; some infants also received extended daily NVP prophylaxis, with or without extended ZDV prophylaxis.

Methods. We analyzed drug resistance in plasma samples collected from all HIV-infected infants whose mothers started HAART in the first postpartum year. Resistance testing was performed using the first plasma sample collected within 6 months after maternal HAART initiation. Categorical variables were compared by exact or trend tests; continuous variables were compared using rank-sum tests.

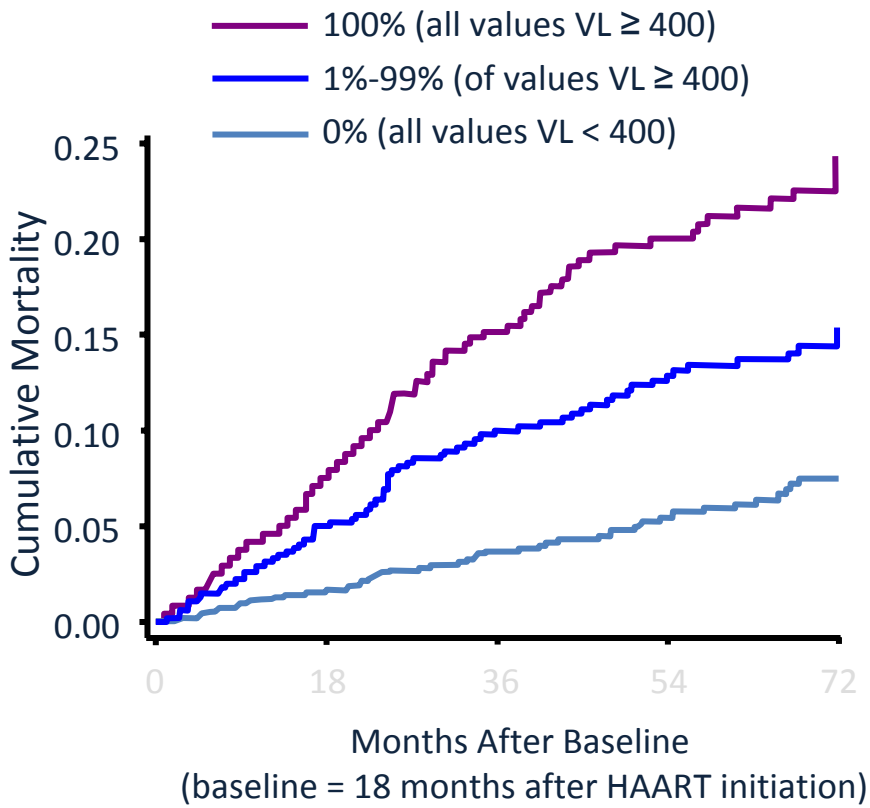
Results. Multiclass resistance (MCR) was detected in HIV from 11 (29.7%) of 37 infants. Infants were more likely to develop MCR infection if their mothers initiated HAART earlier in the postpartum period (by 14 weeks vs after 14 weeks and up to 6 months vs after 6 months, $P = .0009$), or if the mother was exclusively breastfeeding at the time of HAART initiation (exclusive breastfeeding vs mixed feeding vs no breastfeeding, $P = .003$).

Conclusions. postpartum maternal HAART initiation was associated with acquisition of MCR in HIV-infected breastfeeding infants. The risk was higher among infants whose mothers initiated HAART closer to the time of delivery or were still exclusively breastfeeding when they first reported HAART use.

Relationship Between Viral Suppression and Mortality

- Prospective, population-based Danish HIV Cohort Study
  - N = 3919 HIV-infected patients
  - On HAART ≥ 18 months
- Stratified based on proportion of detectable VL (> 400 copies/mL) during the period 6 to 18 months after initiation of HAART
- Higher risk of death with transient or lack of viral suppression
  - Consistent with shorter-term studies

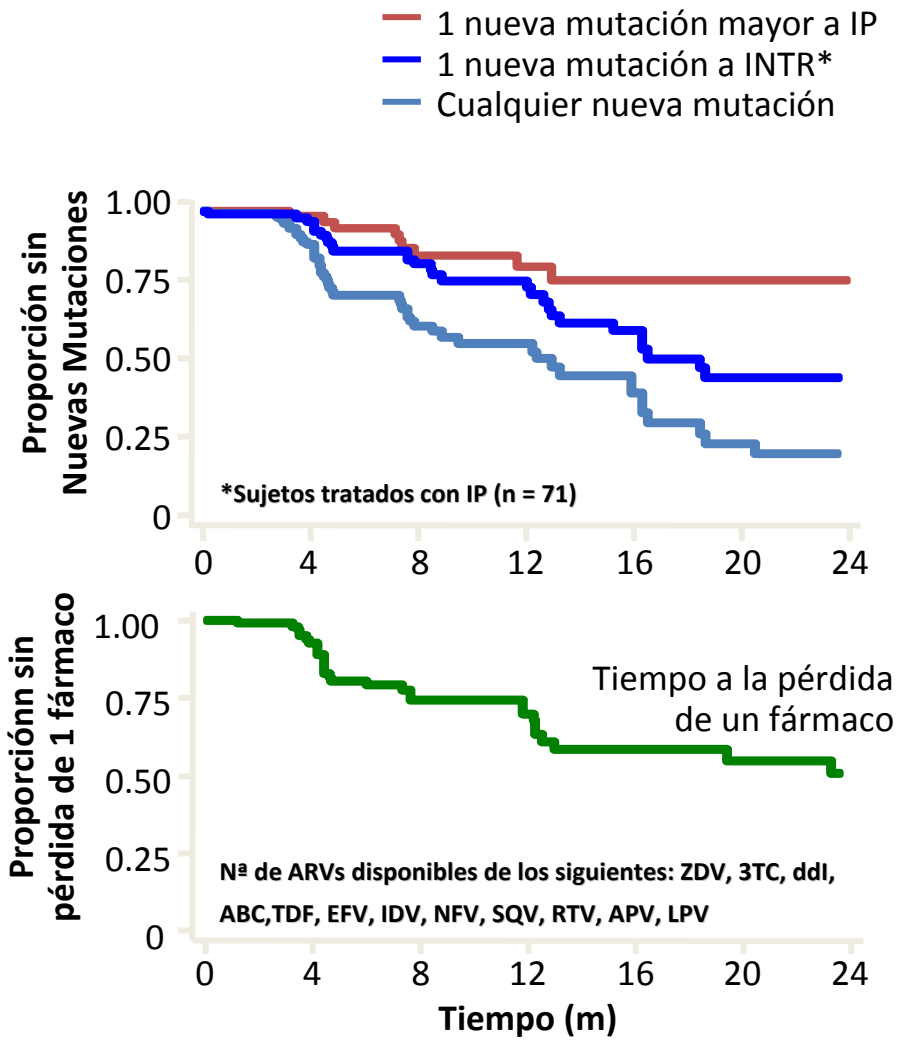
Proportion of Detectable Viral Loads Over 6-18 Months After Initiation of HAART



Lohse N, et al.
CID2006;42:136-144
.

Riesgo de retrasar el cambio con tratamiento no supresivo

- **Cohorte SCOPE de sujetos con experiencia a TAR (n = 106)**
  - **TAR estable ≥ 120 days**
  - **ARN HIV > 1000 c/mL**
  - **≥ 1 mutación resistencia**
  - **Test de resistencia cada 4 m hasta cambio de TAR**
- **Emergencia de nuevas mutaciones al año:**
  - **Cualquier mutación = 44% (95%IC: 33%-56%)**
  - **NAM = 23% (95%IC: 15%-34%)**
  - **IP = 18% (95%IC: 9%-34%)**
- **La viremia persistente comporta el riesgo de limitar las opciones futuras de tratamiento**



Hatano H. CROI 2006.

Prevalence of mutations at 24 and 48 weeks

Overall, prevalence of resistance was higher at 48 compared to 24 weeks.

The proportion of samples with 4-6 TAMS at 24 and 48 weeks was 4% and 39% respectively, all with co-existing M184V

Mutation	Week 24 (n=24)	Week 48 (n=41*)
M184V	15(62%)	32 (78%)
K65R	3 (12%)	6 (15%)
M41L	7 (29%)	17 41%)
D67NG	9 (38%)	23 (56%)
K70R	8 (33%)	23 (56%)
L210W	0 (0%)	3 (7%)
T215FY	7 (29%)	17 (41%)
K219QEN	1 (4%)	9 (22%)
Total TAMs: 0 1-3 4-6	10 (42%) 13 (54%) 1 (4%)	11 (27%) 18 (44%) 12(39%)
TAM Group** I II I and II	5(36%) 4(11%) 5(36%)	2 (7%) 11(37%) 17(57%)

Housenipour: IAC 2007

*excluding 3 patients with BL NRTI resistance
** TAM I=41L, 67NG, 210W, 215Y; TAM II= 67N, 70R, 215F, 219QEN
Note: no MDR mutations /insertions/deletions were observed

Resistencia: definiciones

- ***Resistencia primaria*: resistencia en pacientes naïve de tratamiento**
- ***Resistencia secundaria*: resistencia detectadas en pacientes que han experimentado tratamiento.**

- ***Mutaciones primarias*: aquellas que fueron seleccionadas tempranamente en el proceso de resistencia a una droga. Alto grado de especificidad. Incremento en la IC_{50}**
- ***Mutaciones secundarias:* Tienden a acumularse en el genoma viral que ya tiene una o mas mutaciones primarias. Pueden tener bajo o ningún efecto en el nivel de resistencia (poco o ningún efecto en la IC_{50}). Pueden aumentar la replicación viral mediante el incremento en el fitness viral.**

- **Barrera genética (baja o alta): número de mutaciones necesarias para generar resistencia**
  - **Baja: 3TC (184)**
  - **Alta: ABC (184/65/74/115)**

GENOTIPO Y FENOTIPO

La resistencia a drogas puede ser determinada de dos maneras:

- Resistencia genotípica: término utilizado para describir la presencia de mutaciones que reducen la sensibilidad a una o más drogas.
- Resistencia fenotípica: incremento en la IC_{50} de la droga ensayada.

Ventajas y Desventajas de los ensayos Genotípicos y Fenotípicos

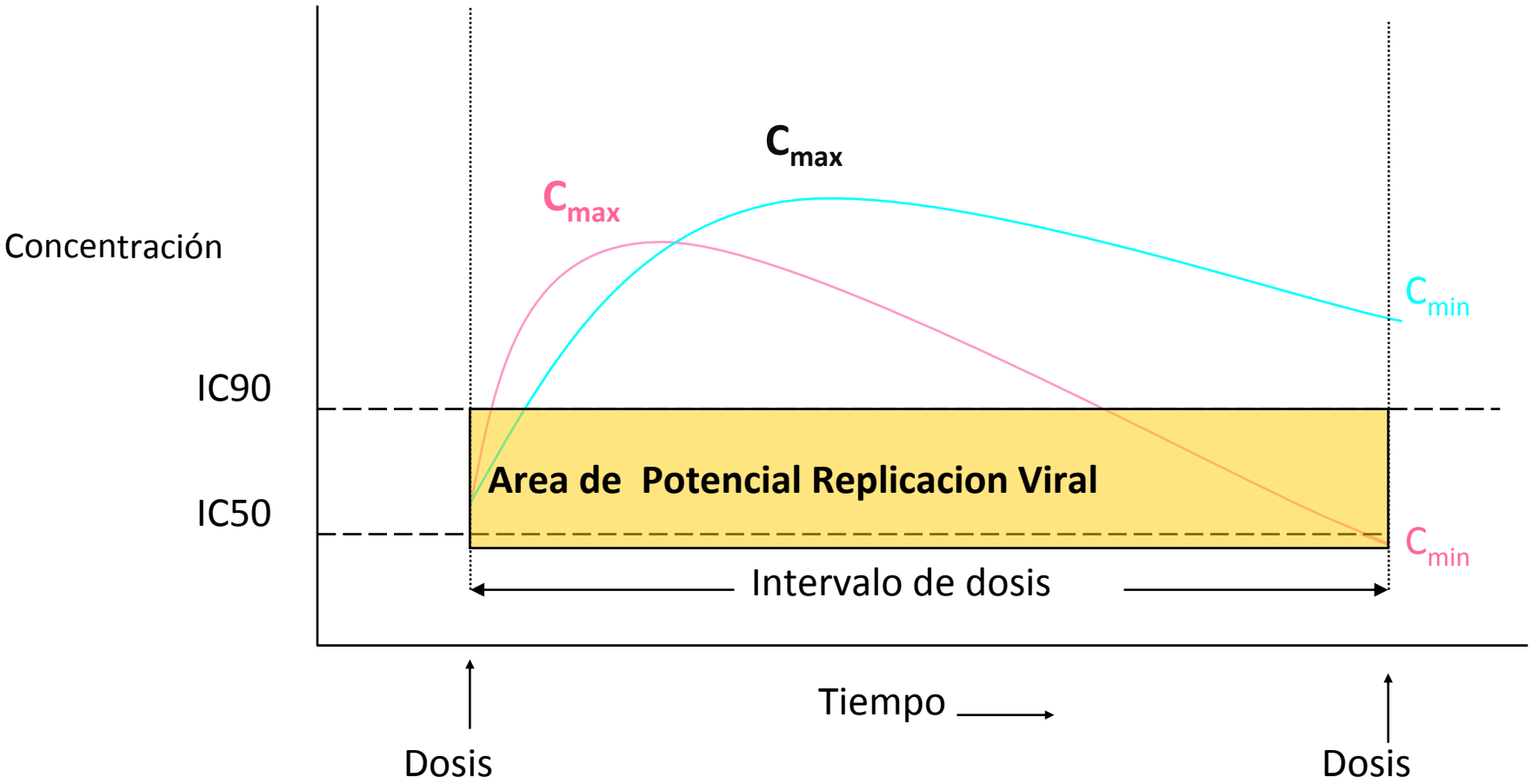
Ensayos Genotípicos

Disponibilidad	Medida indirecta de susceptibilidad.
Rapidez en obtener los resultados	Puede no correlacionar con Fenotipo
Escasos requerimientos técnicos	Interpretación requiere experiencia
Mutaciones preceden resist. fenotipica	Insensible para detectar variant. menores

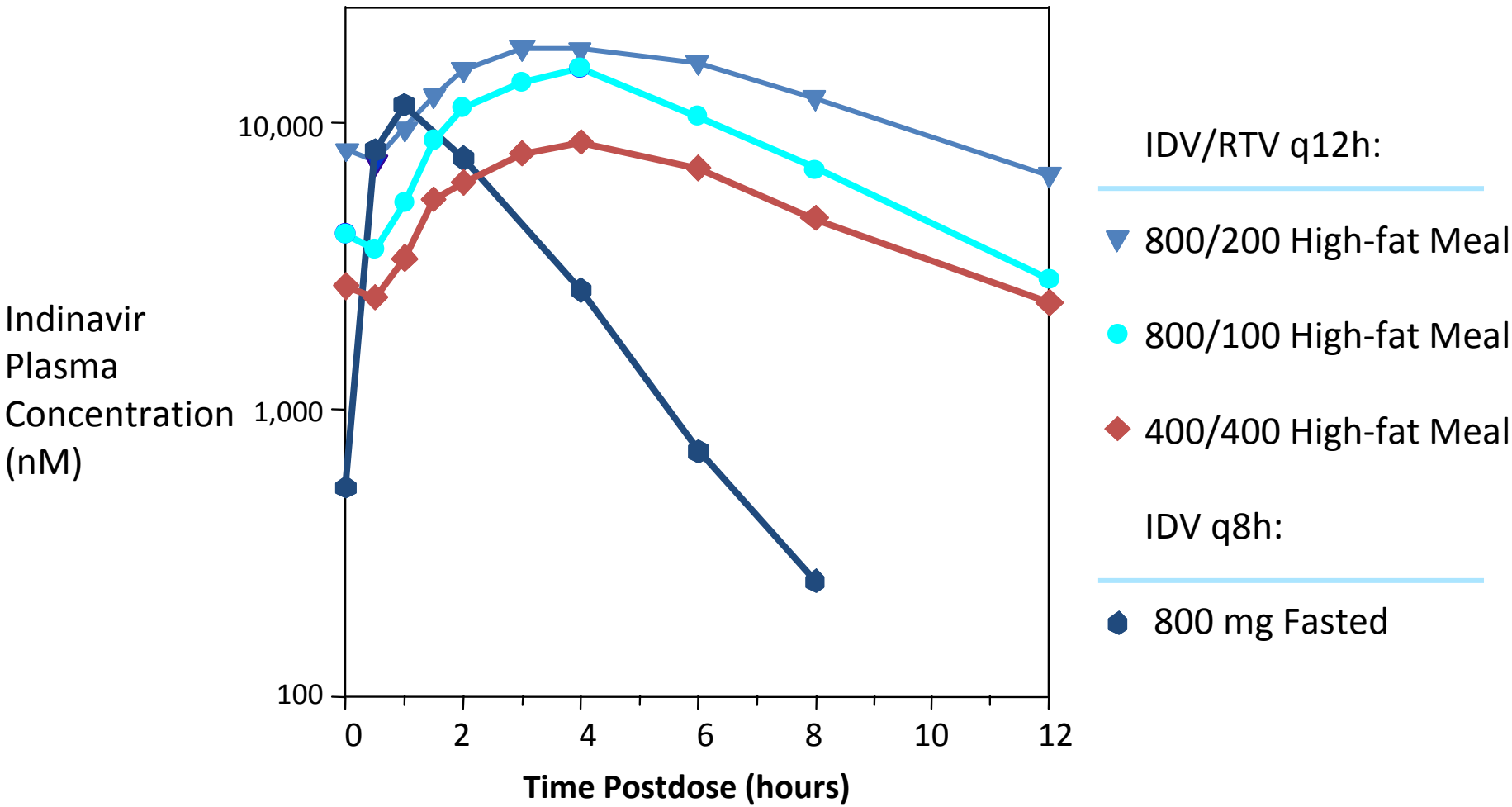
Ensayos Fenotípicos

Medida directa de susceptibilidad	Disponibilidad restringida
Resultados familiares IC50, IC90	Demora en obtener los resultados
	Requerimientos técnicos
	Insensible para detectar variant. menores
	Significancia clínica no determinada

PK


Concentración
C_{max}
C_{max}
C_{min}
IC90
IC50
Area de Potencial Replicacion Viral
C_{min}
Intervalo de dosis
Tiempo
Dosis
Dosis

An Example of Ritonavir Boosting: Indinavir/Ritonavir BID PK Study



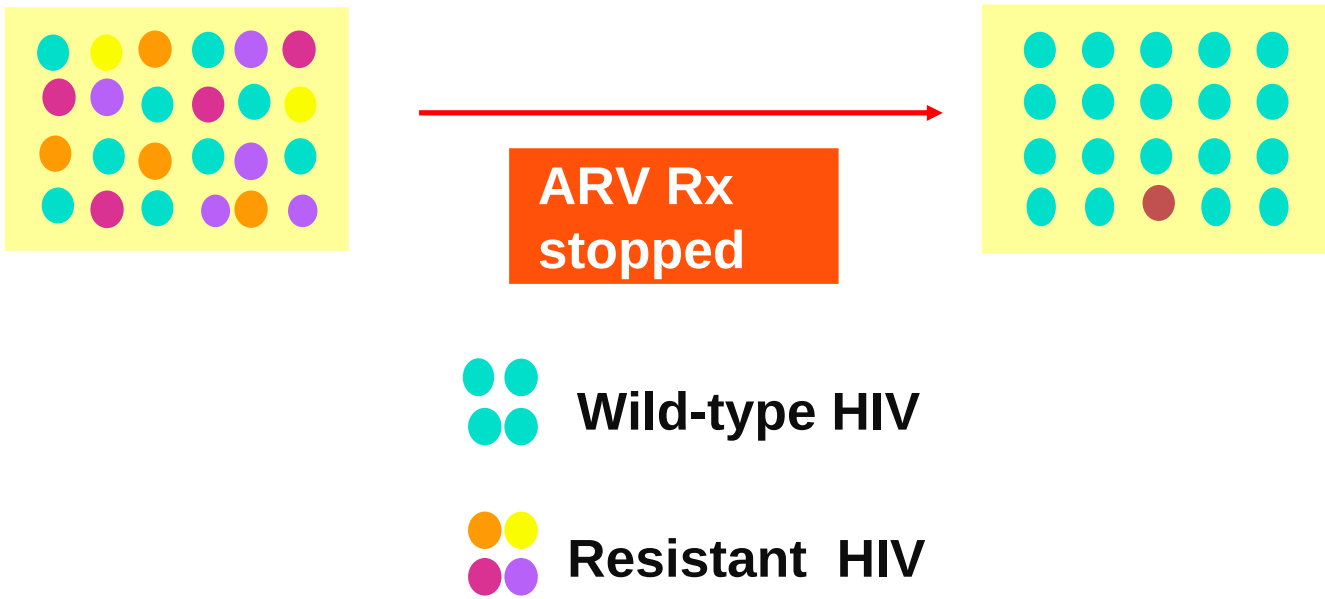
6th Conference on Retroviruses and Opportunistic Infections; 1999. Abstract 362.

HIV Case

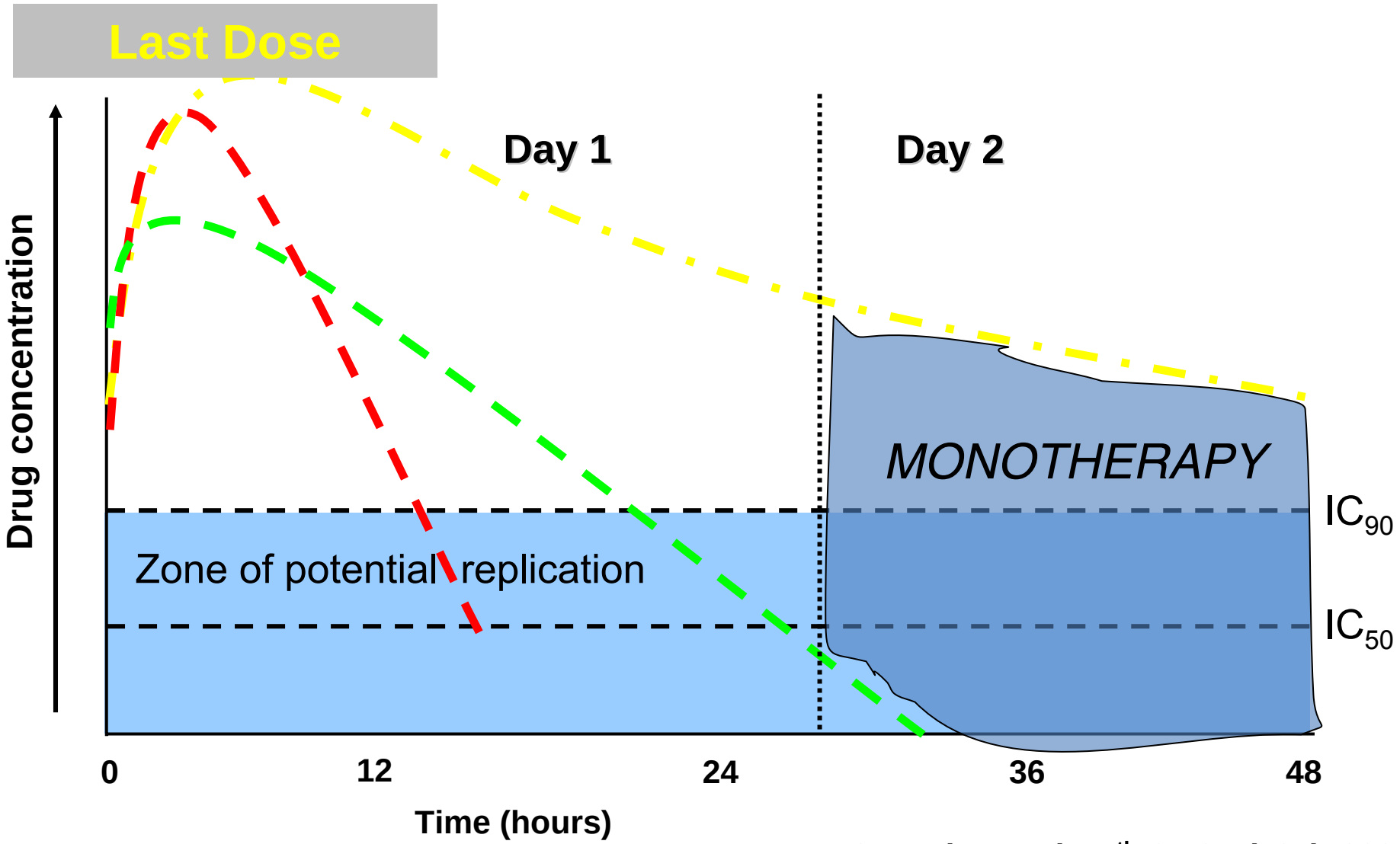
Wild-type HIV

Resistant HIV

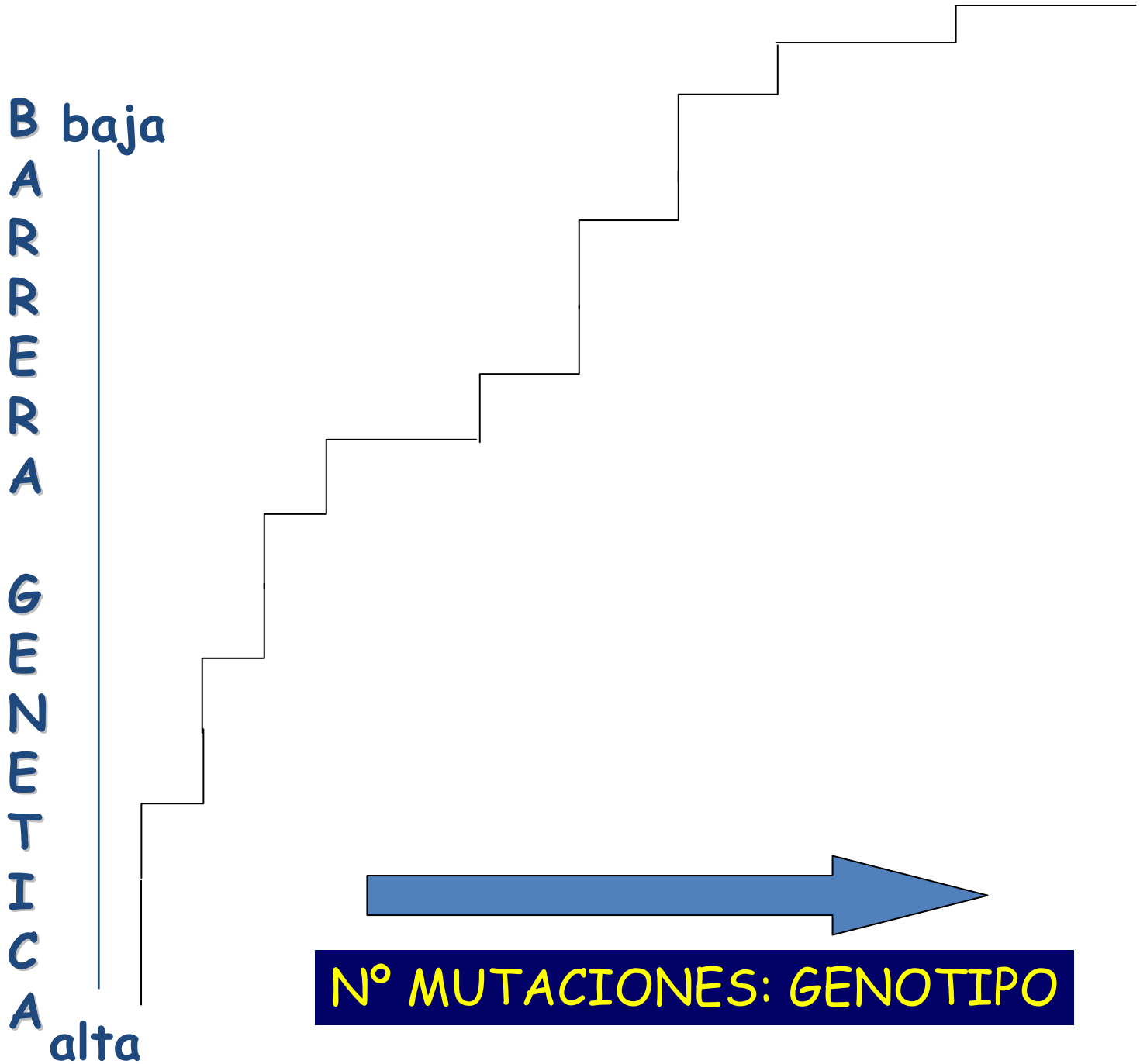
Resistance Testing:
On (Failing) Therapy vs Off Therapy

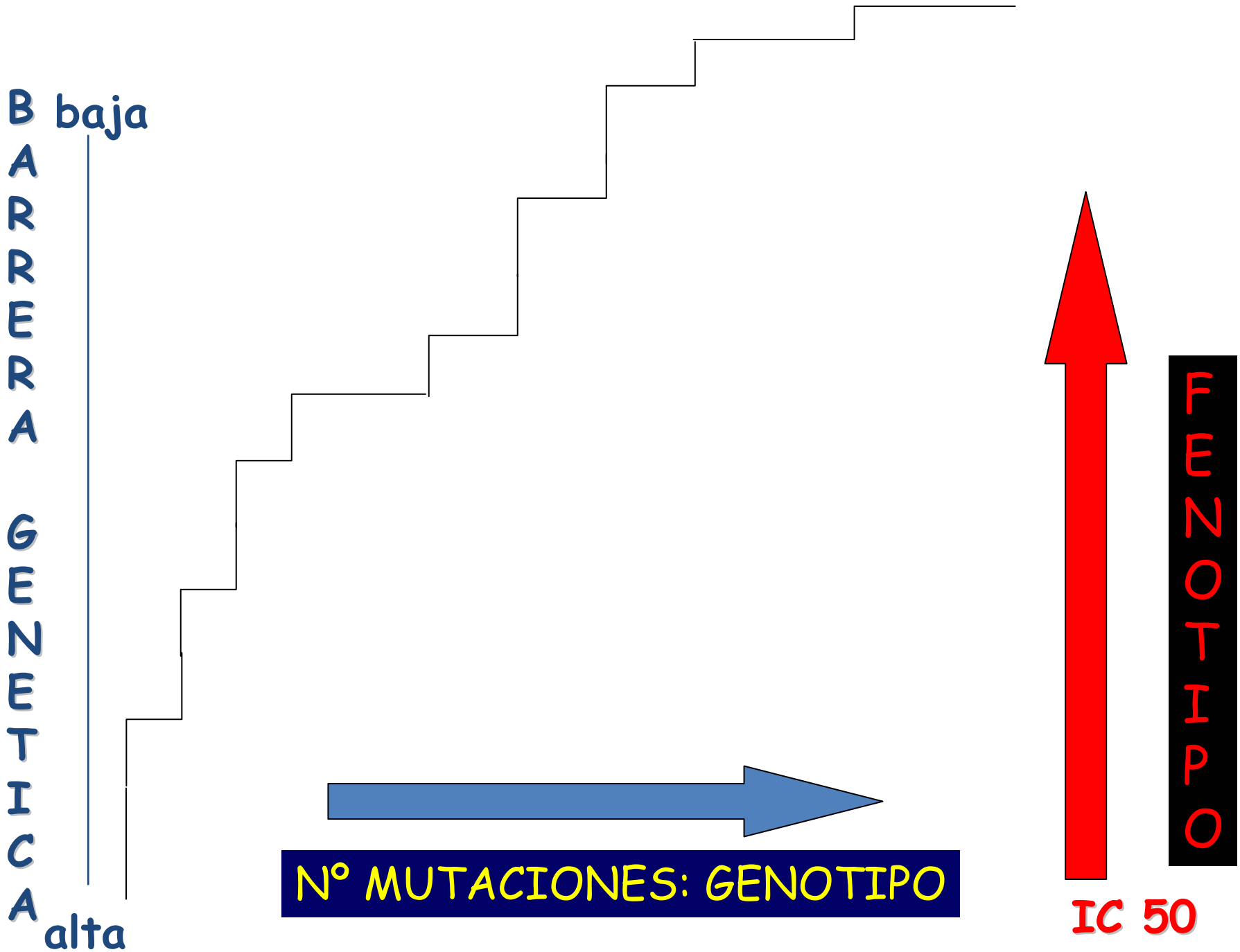


Stopping drugs with different half lives



S. Taylor *et al*. 11th CROI (131), 2004


BARRERA GENETICA
baja
alta
Nº MUTACIONES: GENOTIPO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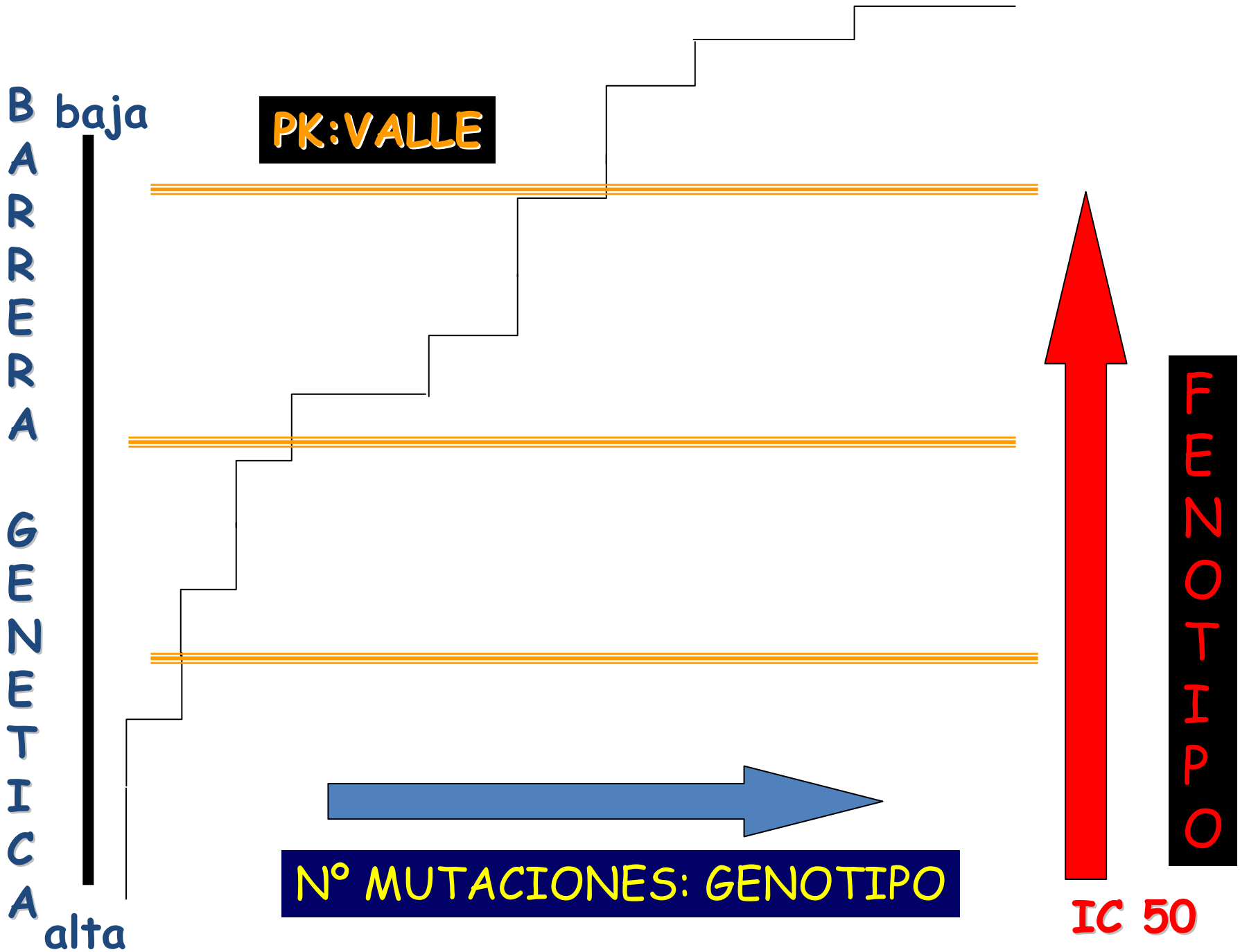
Nº MUTACIONES: GENOTIPO
FENOTIPO
IC 50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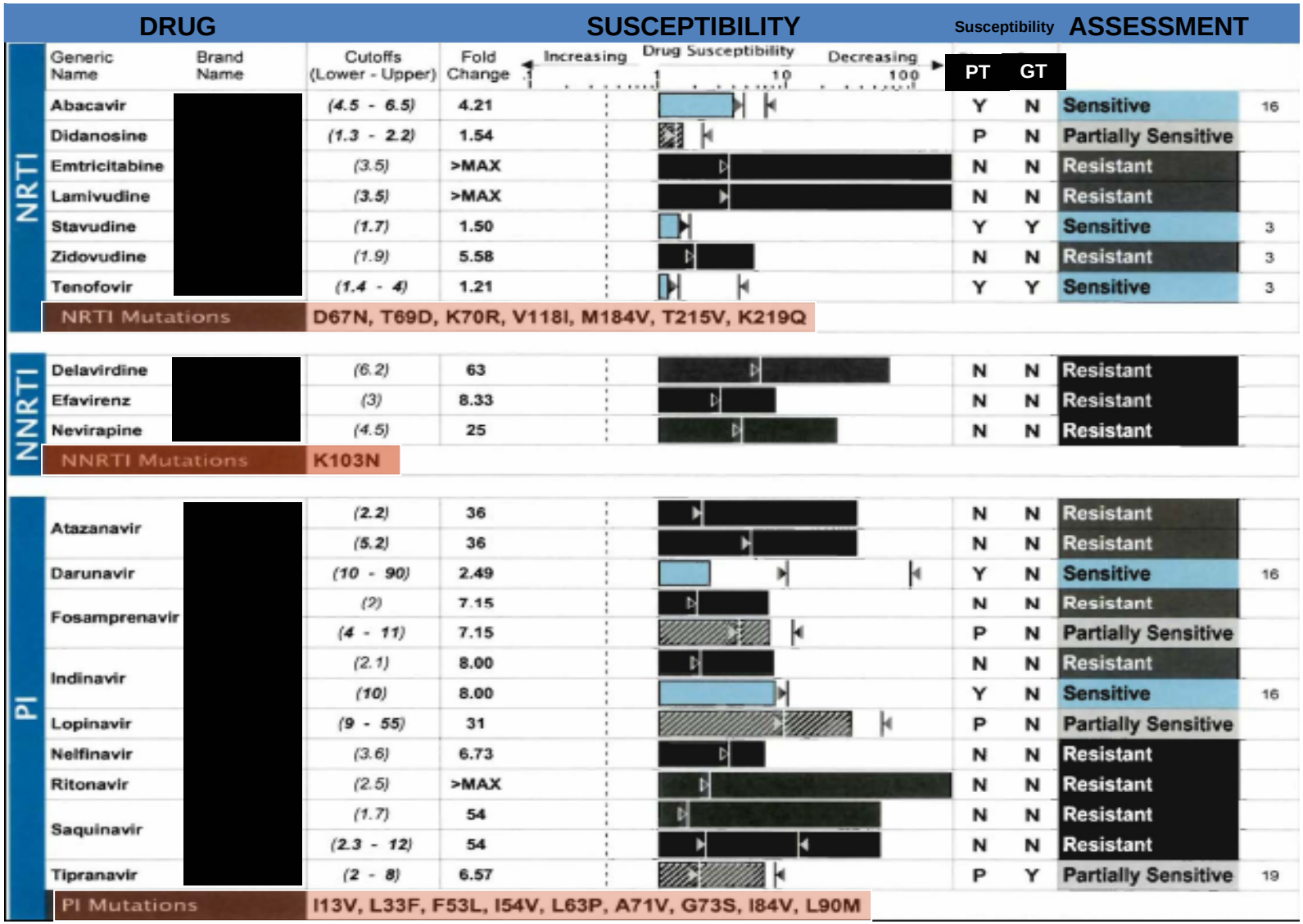
FENOTIPO
IC 50

Test de Resistencia

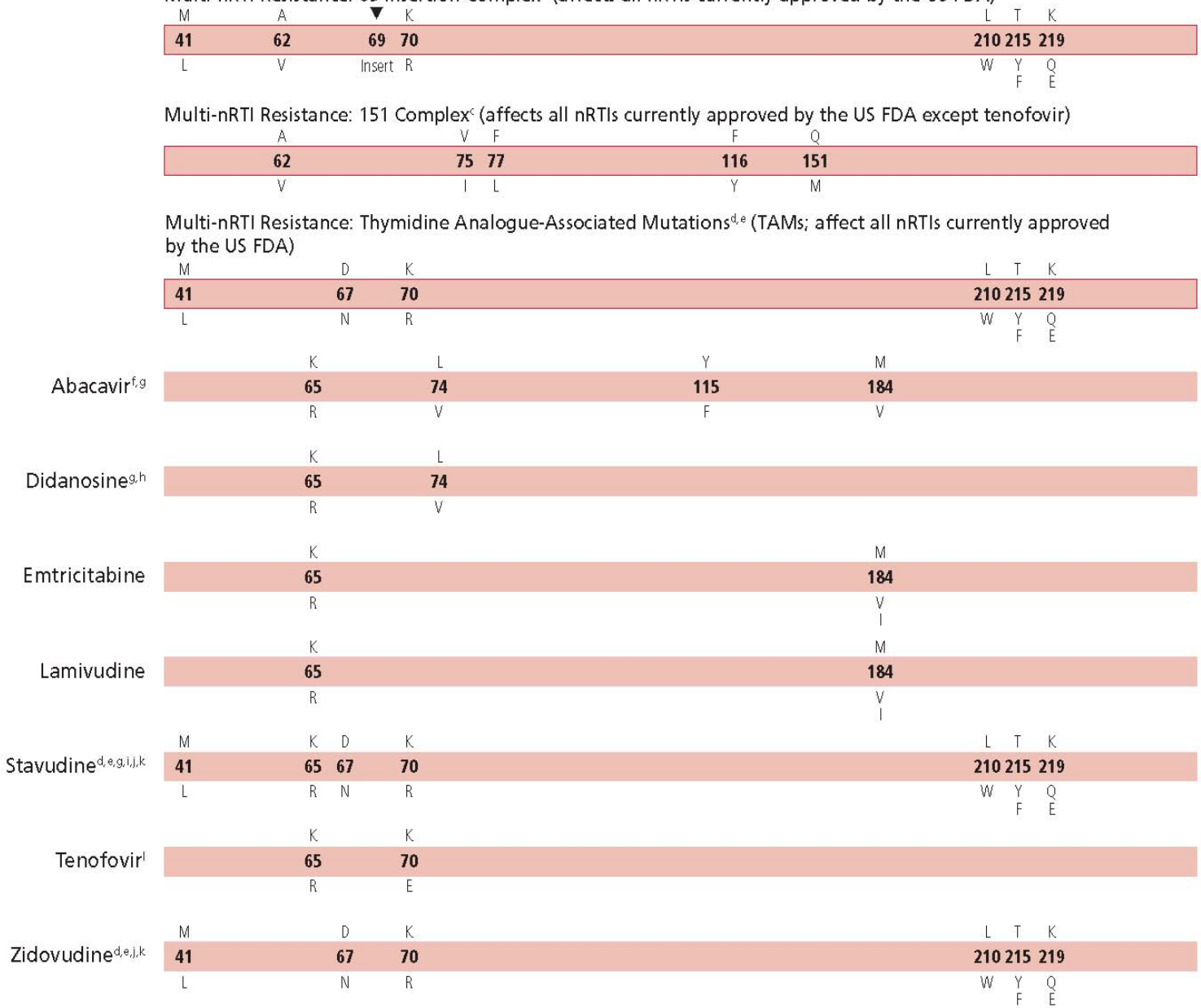


International AIDS Society–USA Topics in HIV Medicine

Special Contribution

Update of the Drug Resistance Mutations in HIV-1: December 2010

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]



Johnson et al. *Topics HIV Med*. December 2009.
Updates available at www.iasusa.org.

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,m]

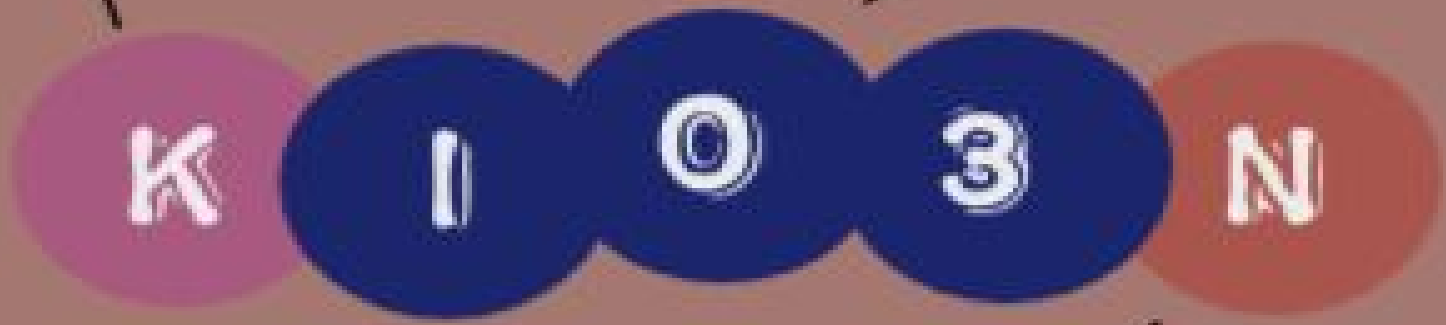
	100	101	103	106	108	181	188	190	225
Efavirenz	L **100** I	K **101** P	K **103** N	V **106** M	V **108** I	Y **181** C I	Y **188** L	G **190** S A	P **225** H

	90	98	100	101	106	138	179	181	190	230
Etravirine[n]	V 90 I	A 98 G	L 100 I[●]	K 101 E H P[●]	V 106 I	E 138 A G K	V 179 D F T	Y 181 C[●] I[●] V[●]	G 190 S A	M 230 L

	100	101	103	106	108	181	188	190
Nevirapine	L **100** I	K **101** P	K **103** N	V **106** A M	V **108** I	Y **181** C I	Y **188** C L H	G **190** A

Código para el aminoácido sustituido

Codón donde se produce la mutación



Codigo para el aminoacido reemplazante (en este caso aspargina por lisina)

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[o,p,q]

Atazanavir +/– ritonavir[r]

Wild type	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Codon	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
Mutation	I F V C	E	R M I T V	I	I	I F V	Q	I L V	I L	V	L	L Y	L V M T A	E	V	L M V	V I T L	C S T A	A T F I	V	V	S	M	L M

Darunavir/ritonavir[s]

Wild type	V	V	L	I	I	I	T	L	I	L
Codon	11	32	33	**47**	**50**	**54**	74	**76**	**84**	89
Mutation	I	I	F	V	V	M L	P	V	V	V

Fosamprenavir/ritonavir

Wild type	L	V	M	I	I	I	G	L	V	I	L
Codon	10	32	46	47	**50**	54	73	76	82	**84**	90
Mutation	F I R V	I	I L	V	V	L V M	S	V	A F S T	V	M

Indinavir/ritonavir[t]

Wild type	L	K	L	V	M	M	I	A	G	L	V	V	I	L
Codon	10	20	24	32	36	**46**	54	71	73	76	77	**82**	**84**	90
Mutation	I R V	M R	I	I	I	I L	V	V T	S A	V	I	A F T	V	M

Lopinavir/ritonavir[u]

Wild type	L	K	L	V	L	M	I	I	F	I	L	A	G	L	V	I	L
Codon	10	20	24	**32**	33	46	**47**	50	53	54	63	71	73	**76**	**82**	84	90
Mutation	F I R V	M R	I	I	F	I L	V A	V	L	V L A M T S	P	V T	S	V	A F T S	V	M

Nelfinavir[t,v]

Wild type	L	D	M	M	A	V	V	I	N	L
Codon	10	**30**	36	46	71	77	82	84	88	**90**
Mutation	F I	N	I	I L	V T	I	A F T S	V	D S	M

Saquinavir/ritonavir[t]

Wild type	L	L	G	I	I	A	G	V	V	I	L
Codon	10	24	**48**	54	62	71	73	77	82	84	**90**
Mutation	I R V	I	V	V L	V	V T	S	I	A F T S	V	M

Tipranavir/ritonavir[w]

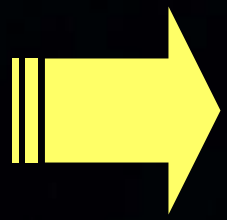
Wild type	L	L	M	K	M	I	I	Q	H	T	V	N	I	L
Codon	10	33	36	43	46	**47**	54	**58**	69	**74**	**82**	**83**	**84**	89
Mutation	V	F	I L V	T	L	V	A M V	E	K R	P	L T	D	V	I M V

Everything You Need to Know About Nucleoside Analog Resistance in One Slide!

Mutation	Selected by	Effects on other NRTIs
184V	3TC, FTC	- Loss of susceptibility to 3TC, FTC - ↓ susceptibility to ABC, ddI (clinically insignificant) - Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF
TAMs	AZT, d4T	- ↓ susceptibility to all NRTIs based on number of TAMs - More resistance with 41/210/215 than 67/70/219 pathway
151M, 69ins	AZT/ddI, ddI/d4T	- Resistance to all NRTIs - T69ins: TDF resistance
65R	TDF, ABC, ddI	- Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC) - ↑ susceptibility to AZT
74V	ABC, ddI	- ↓ susceptibility to ABC, ddI - ↑ susceptibility to AZT, TDF
44D, 118I	AZT, d4T	- Increase NRTI resistance (with 41/210/215 pathway)

Etravirine Resistance Mutations: Weighting of Contribution to ETR Resistance

Mutation	Weight factor
Y181I	3
Y181V	3
K101P	2.5
L100I	2.5
Y181C	2.5
M230L	2.5
E138A	1.5
V106I	1.5
G190S	1.5
V179F[§]	1.5
V90I	1
V179D	1
K101E	1
K101H	1
A98G	1
V179T	1
G190A	1

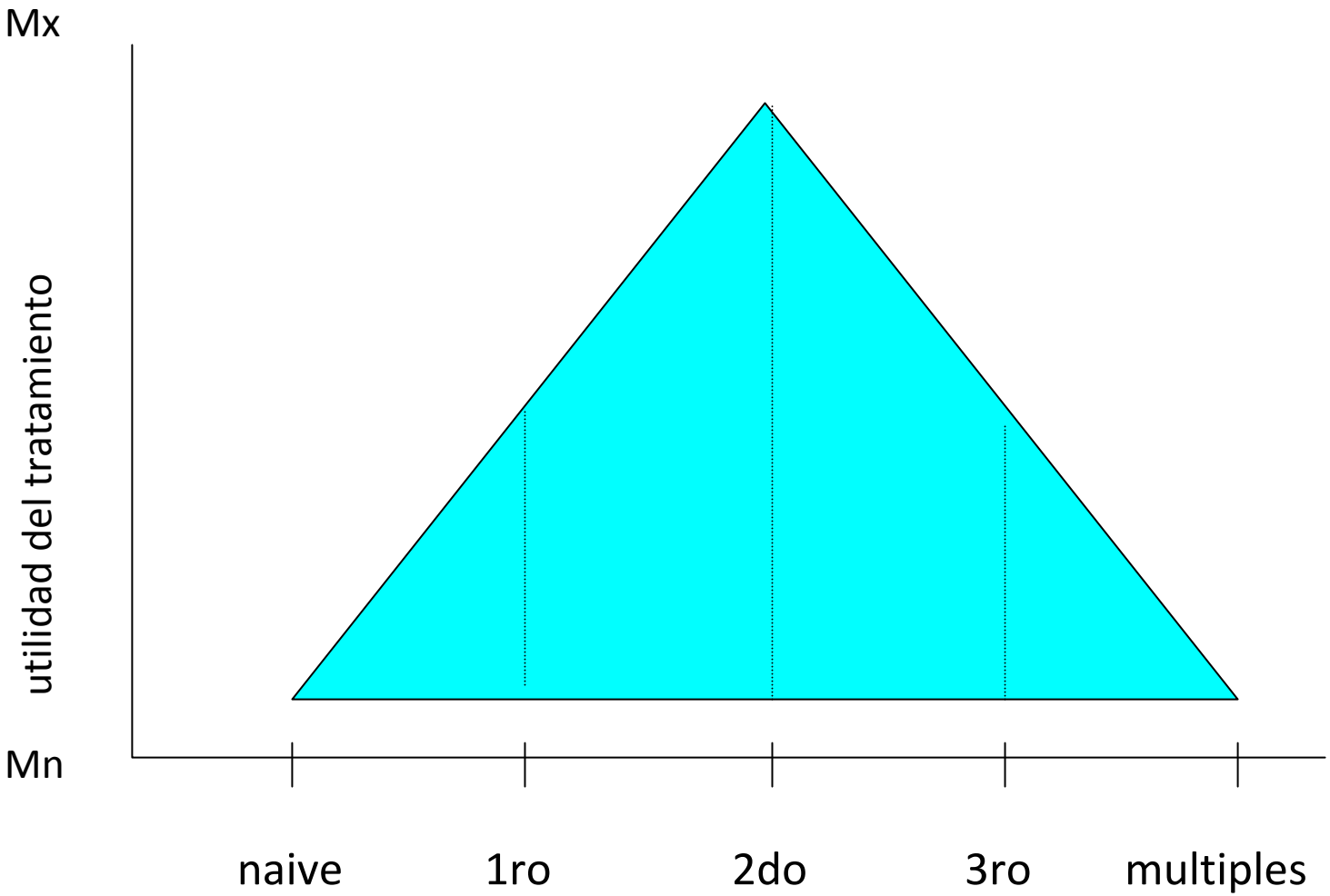


Total weighted score

0–2	Highest response
2.5–3.5	Intermediate response
≥4	Reduced response

Vingerhoets J, et al. 17th IHDRW; Sitges, Spain, June 10-14, 2008; Poster 24.

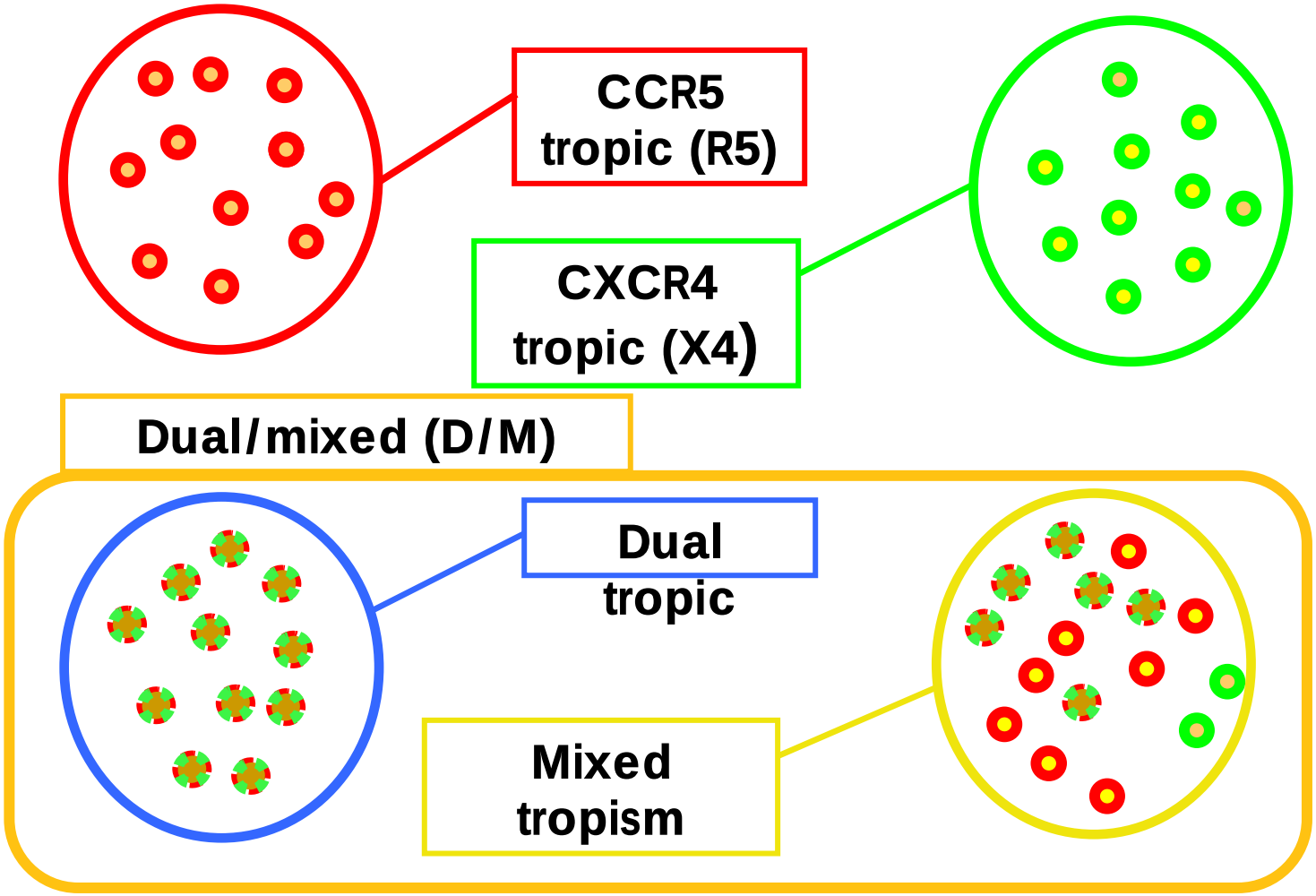
Utilidad de un test según numero de Tx



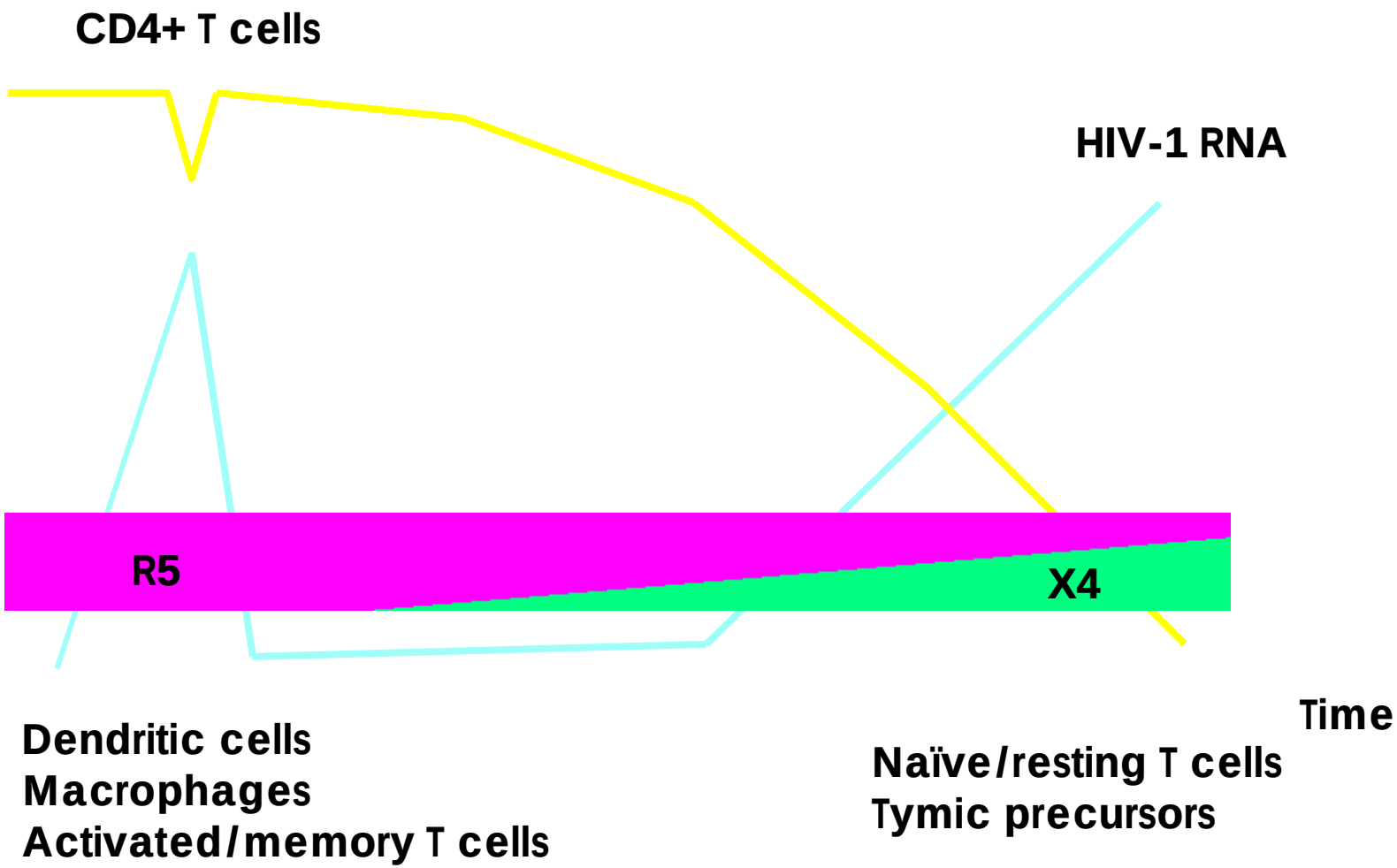
Evaluación del paciente con virus multirresistentes

Deben siempre considerarse las opciones de tratamiento que aparezcan y la necesidad de potenciar el régimen al uso (p.e., riesgo de progresión clínica)

Tropismo


CCR5
tropic (R5)
CXCR4
tropic (X4)
Dual/mixed (D/M)
Dual
tropic
Mixed
tropism

HIV tropism in HIV infection

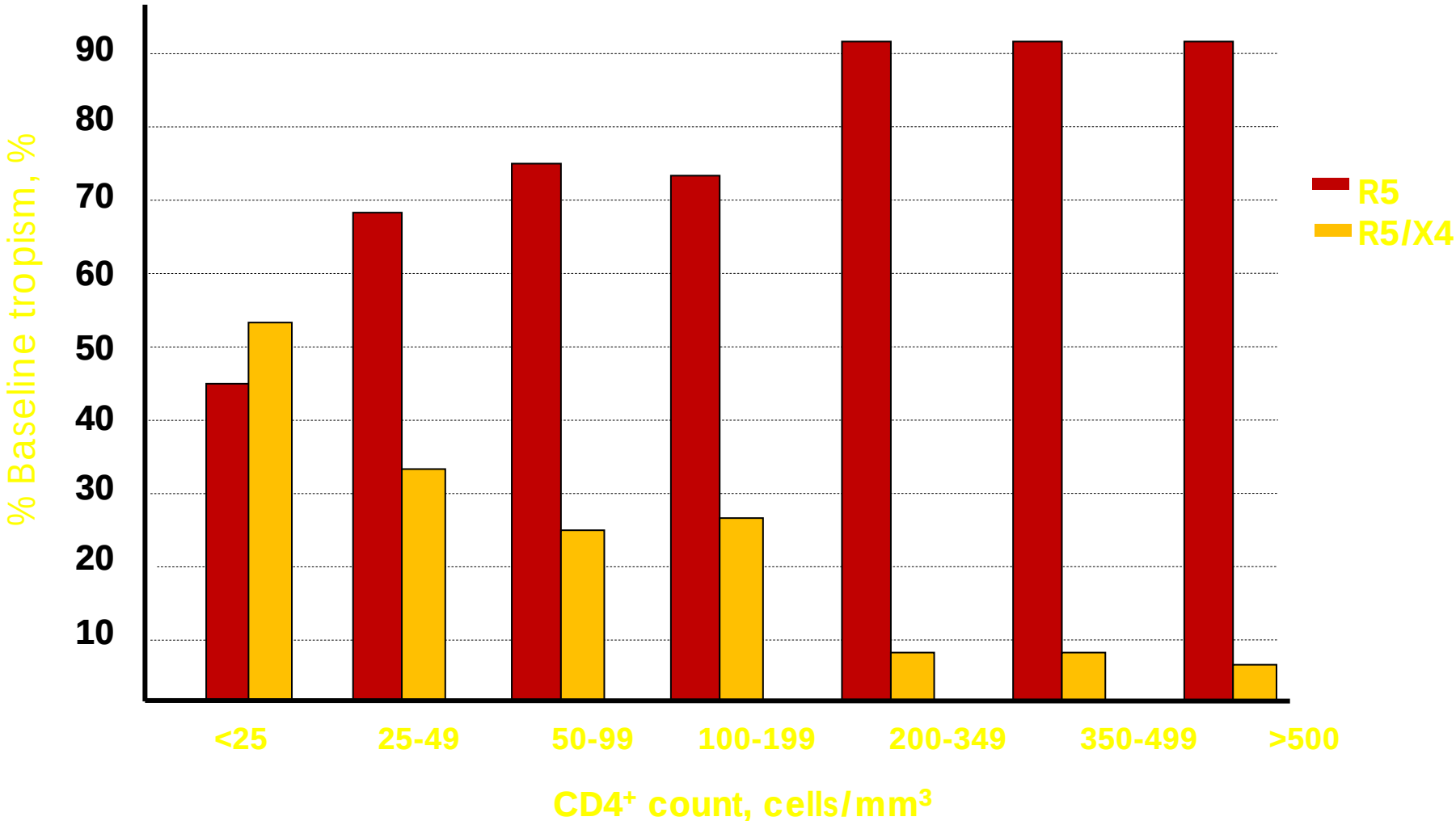


Co-receptor use - prevalence

Study	Treatment	N	R5, %	R5/X4, %	X4, %
Demarest et al [1]	Naïve	325	88	12	0
Brumme [2]	Naïve	979	82	18	0.1
Moyle et al [3]	Naïve	402	81	19	N/A
Hunt et al [4]	Naïve	976	82	18	N/A
Poveda et al [5]	Sc / Naïve	67 / 52	86.6 / 77	13.4 / 23	NA
Demarest et al [1]	pre-treated	117	67	**28**	5
Moyle et al [3]	pre-treated	125	78	**22**	N/A
Hunt et al [4]	pre-treated	182	59	**41**	N/A
Poveda et al [5]	pre-treated	88	64	**36**	N/A
Melby et al [6]	pre-treated	724	50	**48**	2
Wilkin et al [7]	pre-treated	391	49	**47**	4
Hunt et al [8]	pre-treated	76	68	**18**	3
Lehmann et al [9]	pre-treated	40	53	**30**	N/A

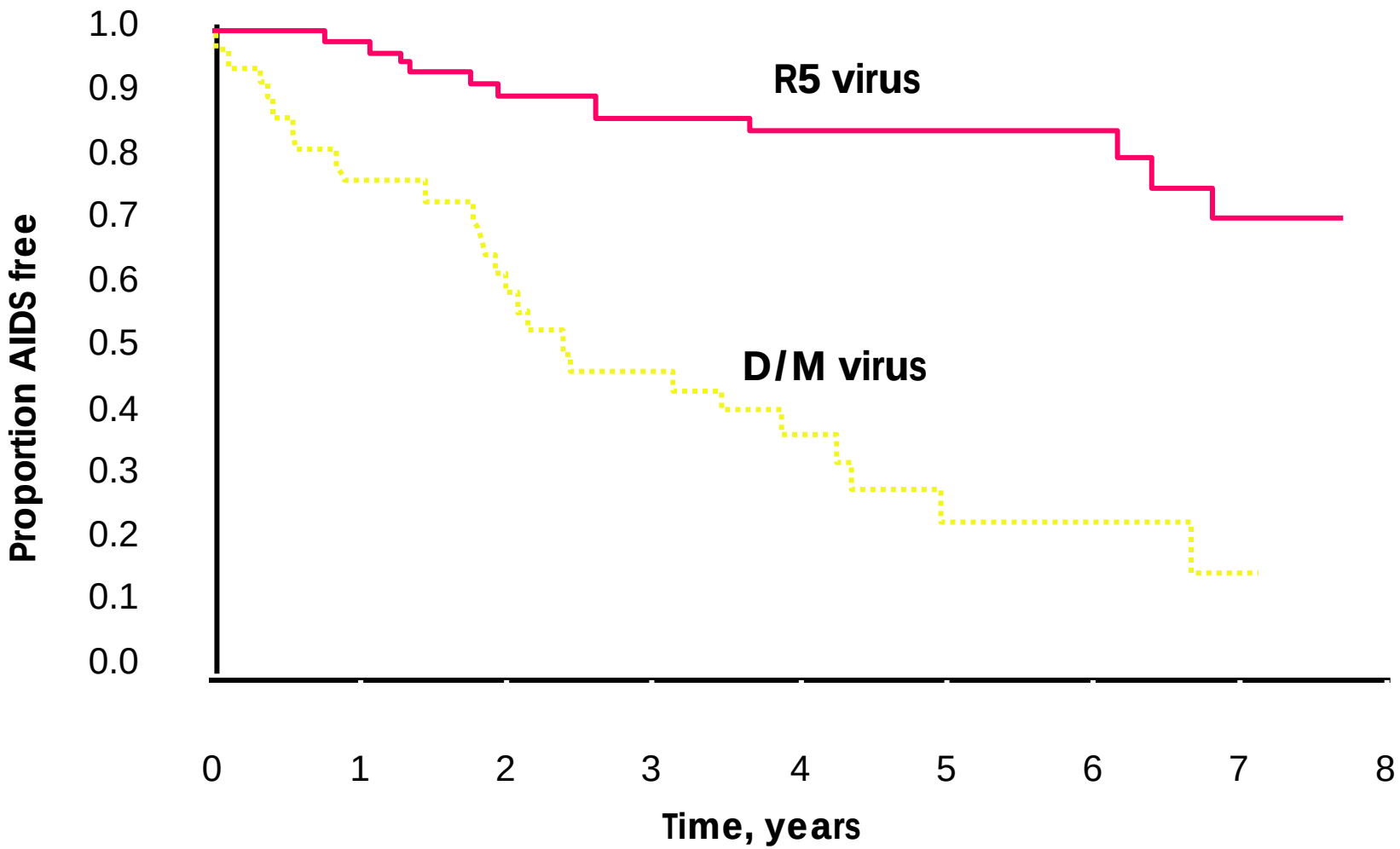
1.Demarest et al. ICAAC 2004. Abstract H-1136; 2.Brumme et al. J Infect Dis. 2005;192:466-74; 3.Moyle et al. J Infect Dis. 2005;191:866-72; 4.Hunt et al. J Infect Dis. 2006;194:926-30; 5.Poveda et al. J Med Virol 2007;79;1040-6; 6.Melby et al. CROI 2006. Abstract 233; 7.Wilkin, et al. CROI 2006. Abstract 655; 8.Hunt et al. CROI 2007. Abstract 619; 9.Lehmann et al. J Clin Virol. 2006;37:300-4.

HIV tropism *vs* CD4 counts



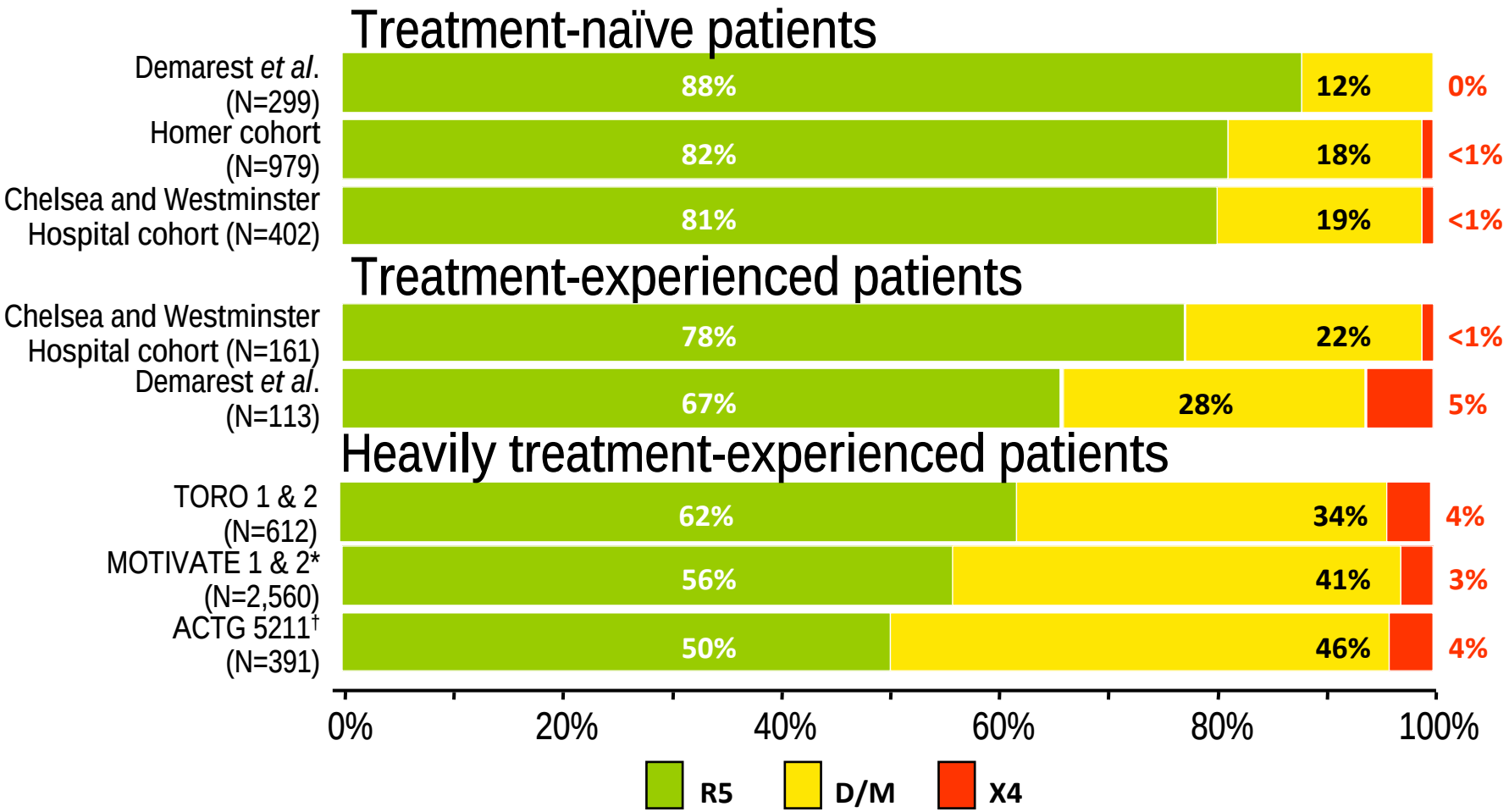
Brumme, et al. JID 2005; 192:466-474

HIV tropism & disease progression



Daar, et al. CID 2007; 45:643-9

Prevalence of R5, X4 or DM according to ARV experience



ARV multi experienced patients have been infected by longer periods of time, therefore, with great odds of harboring X4.

Indicaciones de los test de Resistencia

- Infeccion aguda
- Infección crónica, evaluación inicial
- Fallo
- Embarazo
- Nunca con tratamiento suspendido

Low-Frequency HIV-1 Drug Resistance Mutations and Risk of NNRTI-Based ART Failure

Objective To evaluate the association of preexisting drug-resistant HIV-1 minority variants with risk of first-line nonnucleoside reverse transcriptase inhibitor (NNRTI)–based antiretroviral virologic failure.

Individual data from 10 studies and 985 participants were available for the primary analysis. Low-frequency drug resistance mutations were detected in 187 participants, including 117 of 808 patients in the cohort studies. *Low-frequency HIV-1 drug resistance mutations were associated with an increased risk of virologic failure (hazard ratio (HR], 2.3 [95% confidence interval {CI}, 1.7-3.3]; P < .001) after controlling for medication adherence, race/ethnicity, baseline CD4 cell count, and plasma HIV-1 RNA levels. Increased risk of virologic failure was most strongly associated with minority variants resistant to NNRTIs (*HR, 2.6 [95% CI, 1.9-3.5]; *P* < .001). Conclusion Low-frequency HIV-1 drug resistance mutations, particularly involving NNRTI resistance, were significantly associated with a dose-dependent increased risk of virologic failure with first-line ART.

Lii et al: JAMA 2011

Limitaciones de *todos los t*ests

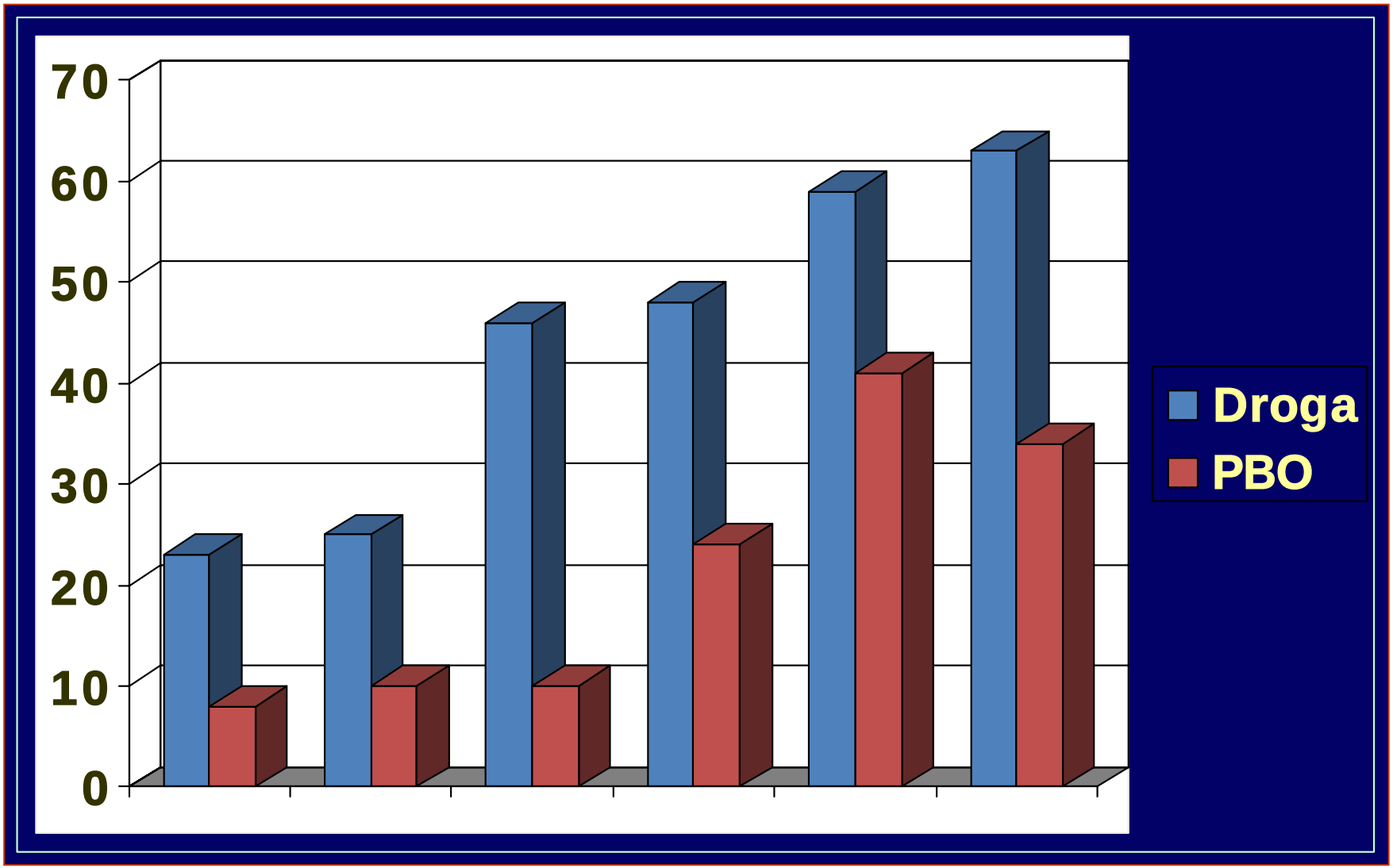
- No detecta poblaciones minoritarias (<20%?)
- No detecta resistencia archivada en reservorios
- Util para excluir mas que para incluir drogas
- Los resultados mas confiables vinculados al régimen actual
- Requiere un mínimo de carga viral

Los resultados obtenidos en los ensayos genotípicos y/o fenotípicos deben ser interpretados dentro del contexto del tratamiento actual y de los tratamientos previos del paciente.

Estudios iniciales de terapia de rescate

Estudio	N	Tratamiento	Resultados CV
A333 Para JID 2000	72	SQV→IDV	37% <200 w8
A359 Gulick JID 2000	277	IDV→RTV/SQV or RTV/ NFV + DLV, ADV, or both	30% <500 w16
A372b Hammer AVT 03	84	IDV→EFV/ADV±ABC± NFV	35% <500 w16
Tebas AIDS 1999	26	NFV→RTV/SQV	54% <500 w48
2007 Ait-Khaled AVT 03	99	PI→ABC/EFV/APV	26% <400 w16
A398 Hammer JAMA 02	481	PI→APV/ABC/EFV/ADV±PI	31% <200 w24

EFICACIA VIROLOGICA (<50 copias)



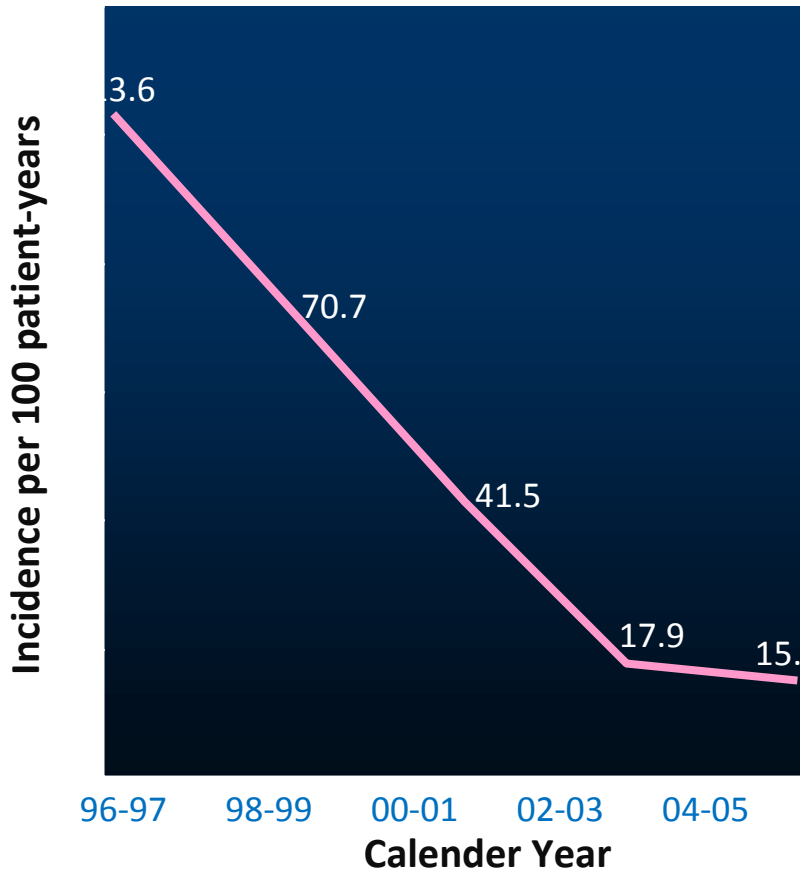
TORO RESIST POWER MOTIVATE DUET BENCHMRK

[1]Nelson M. JAIDS 2005. [2]Hicks C. ICAAC 2004. [3]Hill A & Moyle G. 12th BHIVA 2006. [4]Lazzarin A. XVI IAC, 2006. [5]Nelson M. 14th CROI, 2007. [6]Lalezari J. 14th CROI, 2007. [7]Clotet B. Lancet 2007 [8]Cooper D. 14th CROI, 2007. [9]Steigbigel R. 14th CROI 2007.

NA-ACCORD: (33,381 patients on HAART)

Trends in Second HAART Failure

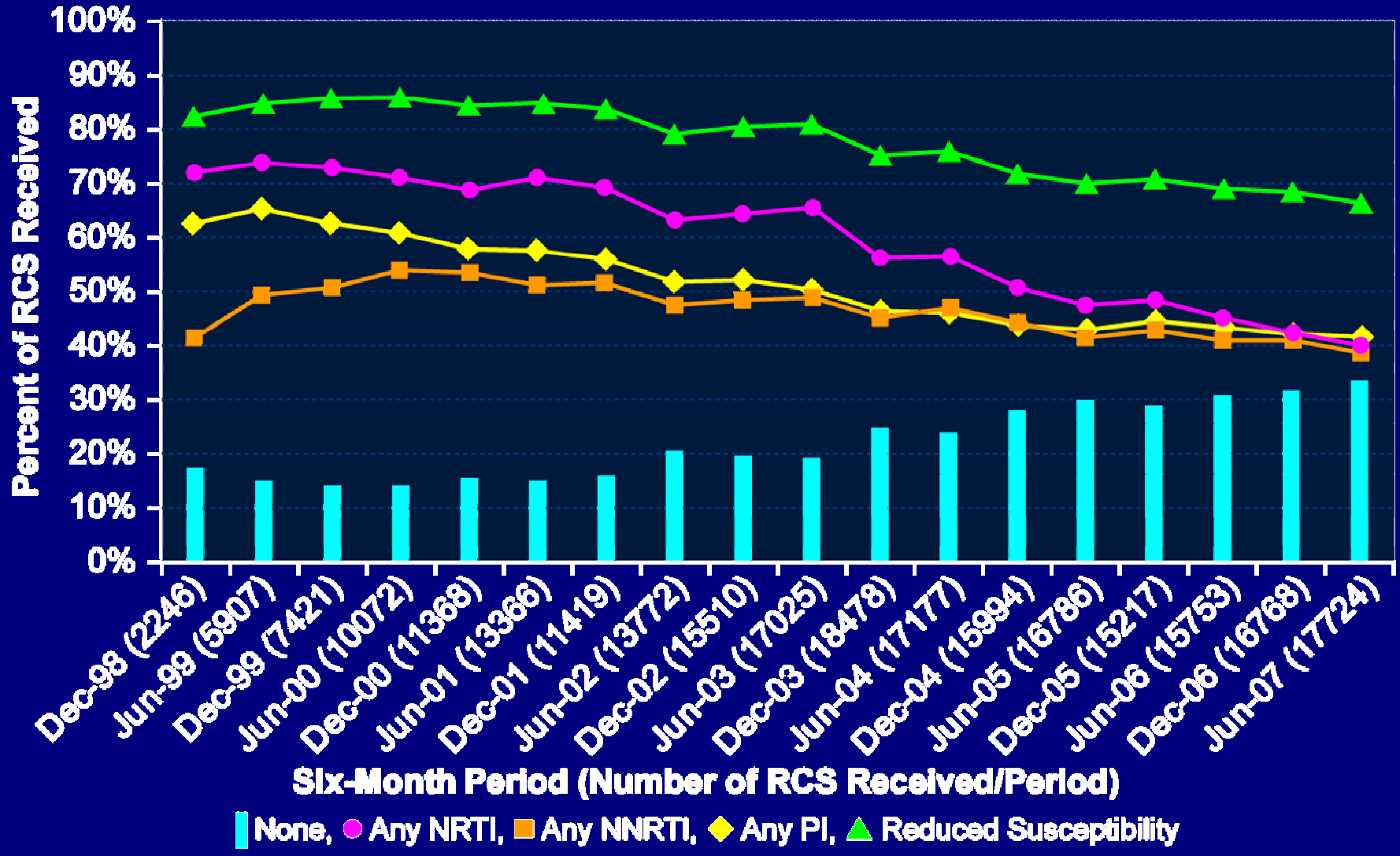
- **Adjusted relative risk of second virologic failure has declined dramatically**
  - **Decreased from 1.46 (96-97) to 0.54 (04-05) per 100 patient-years**
- **No improvement in mortality following second virologic failure**
  - **Median survival: 7.1 years**
- **Independent risk factors associated with increased risk of death**
  - **CD4 cell count and HIV RNA level at time of second virologic failure**
  - **No association**
    - **Prior treatment exposure**
    - **Pre-HAART**



***Adjusted for time from HAART initiation, sex, age, AIDS, CD4, and HIV RNA at HAART initiation and switch, and type of HAART).**

Deeks S, et al. 15th CROI. Boston, 2008. Abstract 41.

Nine-year Phenotypic Trends for Fully Susceptible (Bars) and Reduced Susceptibility (Lines) as a Proportion of RCS Received (n:> 230,000)



Sista, et al. J.Clin Virol. 44: 190 (2009)

CONFRONTANDO EL FALLO:

- Objetivo: Supresion virologica, < 50 copias/mL
- Como: Usar al menos 2 drogas nuevas, en lo posible una clase nueva
- Cuando: Lo antes posible, ante un fallo confirmado
- Por que?:
  - Evitar la acumulacion de mutaciones (GSS)
  - Evitar cambios en la IC 50 (PSS)
  - Preservar drogas activas en el OBR
  - Preservar y recuperar CD4
  - Reducir la morbimortalidad