



## VII Sesiones Clínicas GEVIHSS-IAPAC

Oaxaca de Juárez, México, Marzo 2010

# Presencia de Mutaciones Asociadas al VIH en pacientes sin Tratamiento Previo

Mesa redonda: PERDIDA DE LA SUSCEPTIBILIDAD DEL VIH A LOS FARMACOS ARVs

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# Resistencia a ARV: Definiciones

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- **RESISTENCIA PRIMARIA**

Resistencia a ARV presente antes de inicio de tratamiento

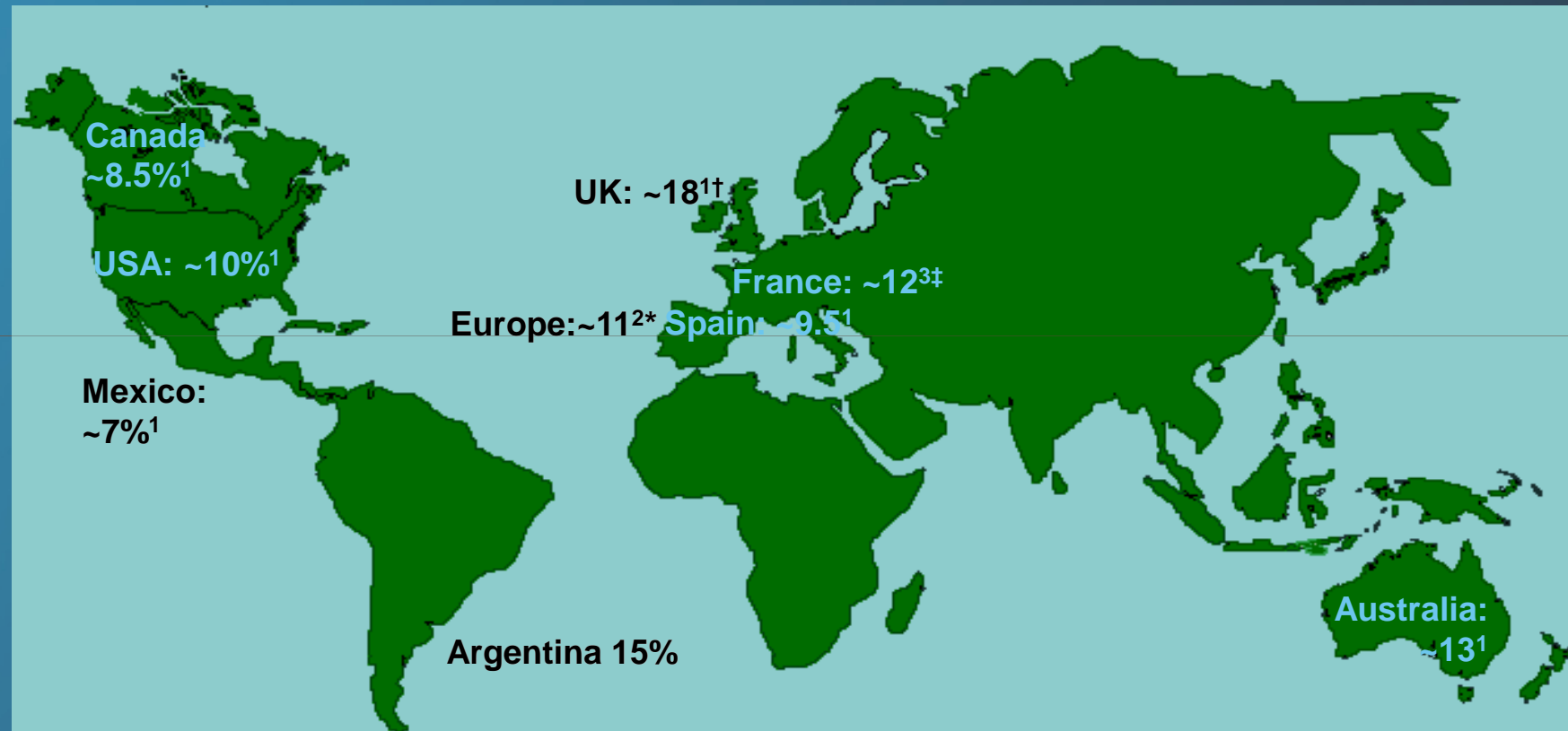
- Polimorfismos: Variación natural del virus
  - ◆ Poco significativa clínicamente
  - ◆ L63P
- Resultado de transmisión de cepas resistentes
  - ◆ Puede comprometer el éxito del tratamiento

- **RESISTENCIA SECUNDARIA**

Resistencia a ARV presente después de falla a tratamiento y responsable de esta

# Resistencia Primaria

% de nuevas infecciones por VIH con resistencias primarias

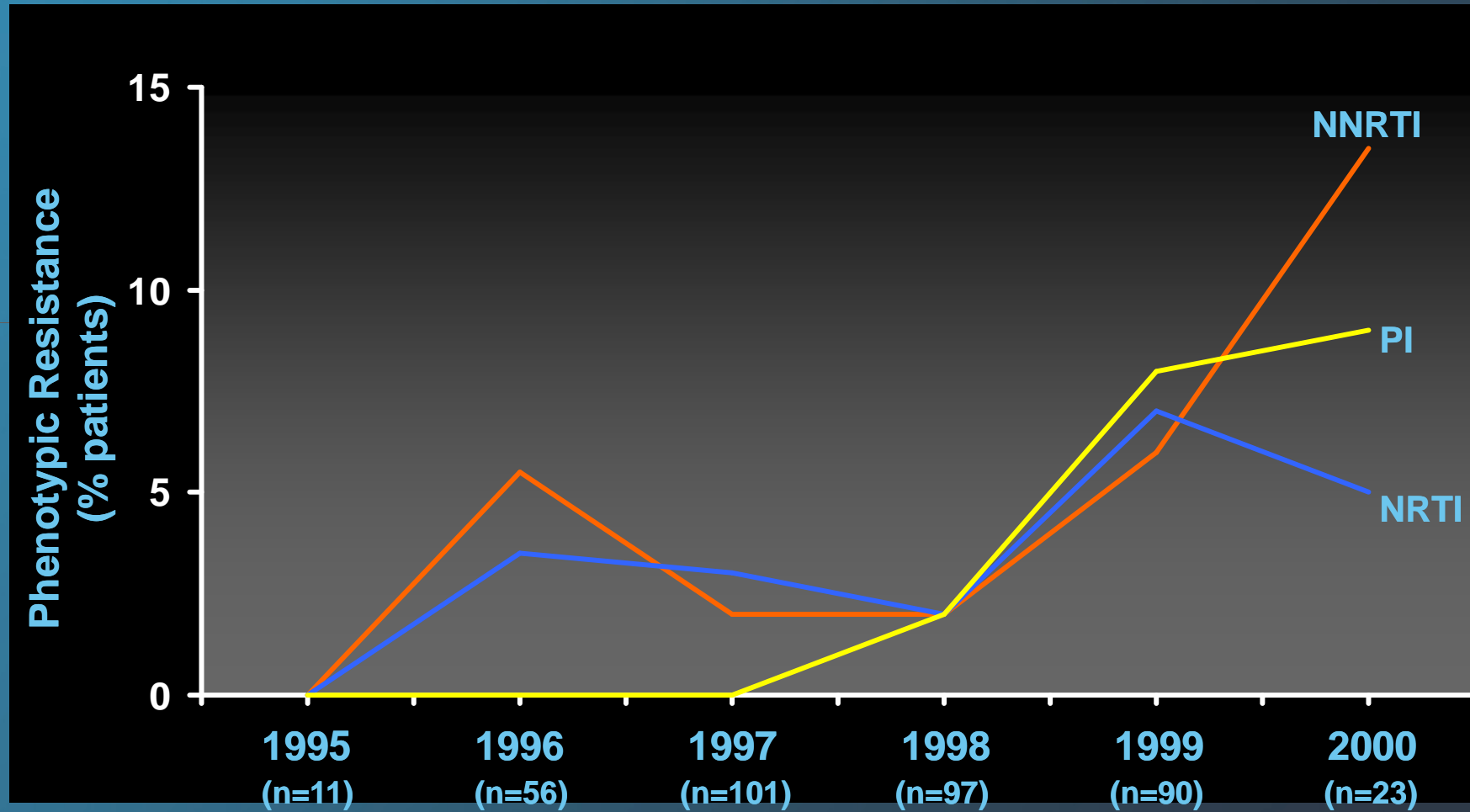


<sup>1</sup> XIII IHDRW, Tenerife, June 2004; <sup>2</sup> Wensing AMJ, XII IHDRW, June 2003, #117;

<sup>3</sup> Delfraissy JF, Rapport 2004

# Drug-Resistant HIV in Treatment-Naïve Patients

IC<sub>50</sub> >10-fold increase via PhenoSense HIV (ViroLogic)



Little SJ, et al. *N Engl J Med.* 2002;347:385-394.

## Transmitted Resistance Mutations in Recently Infected Subjects: 1996-2002

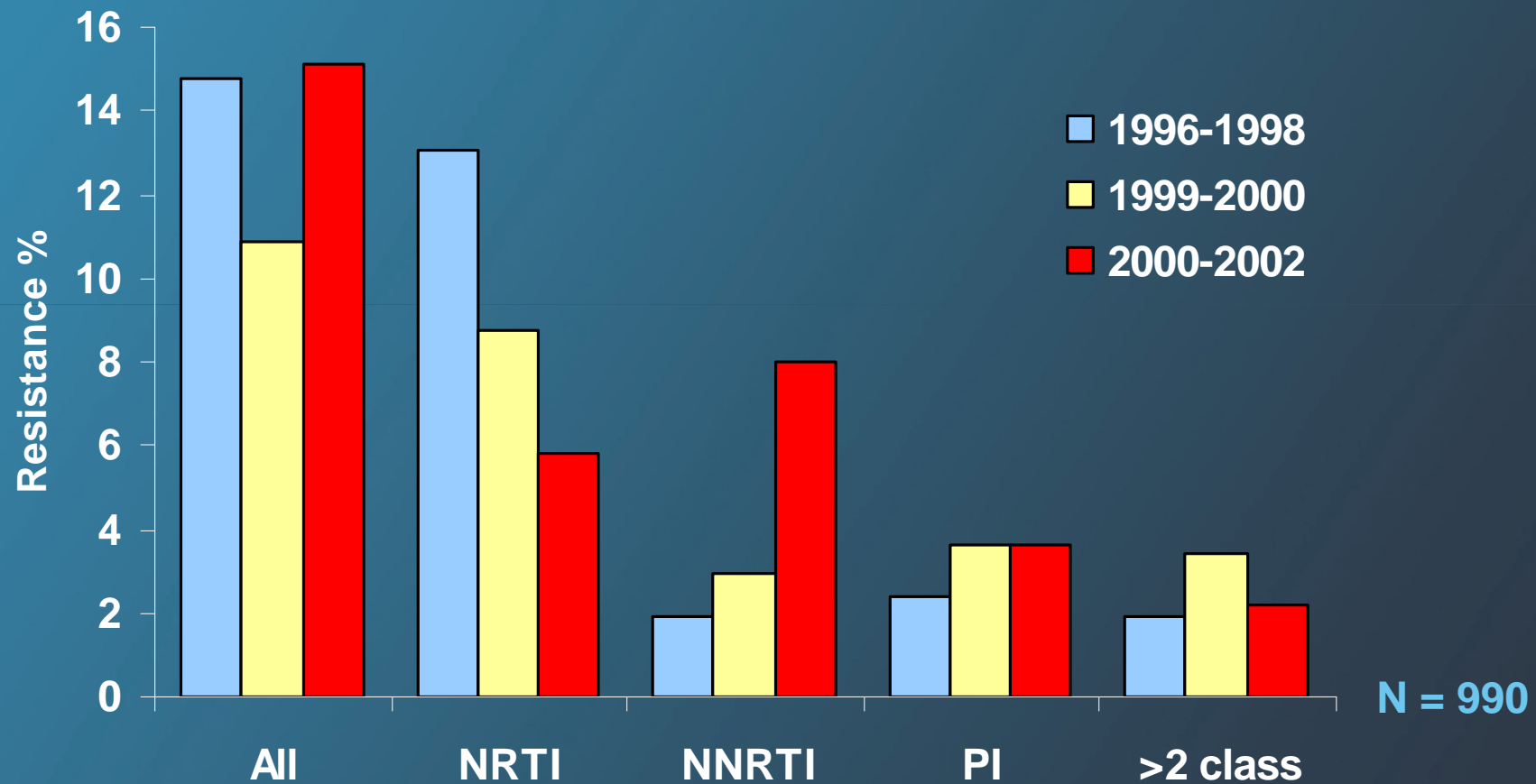
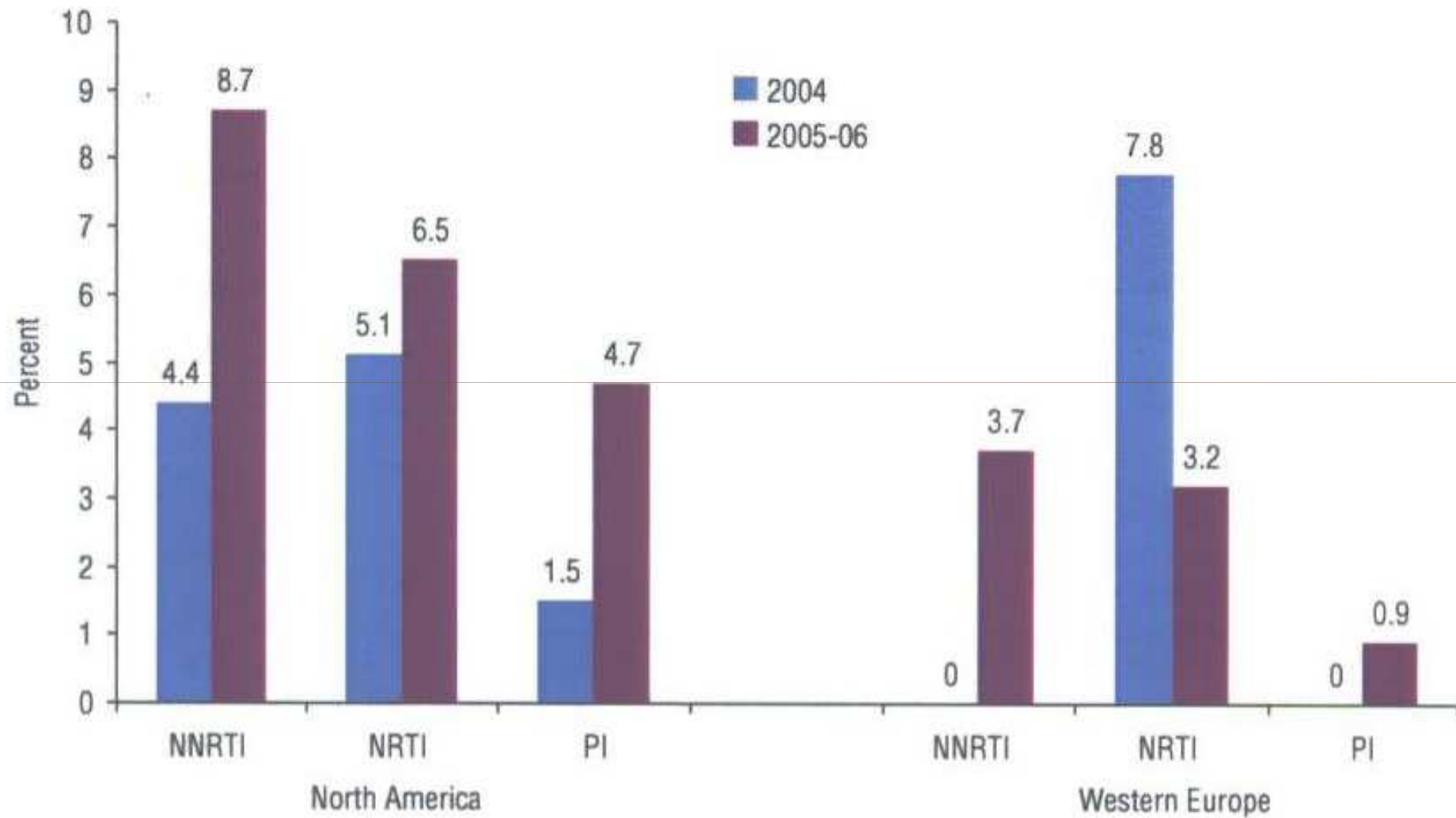
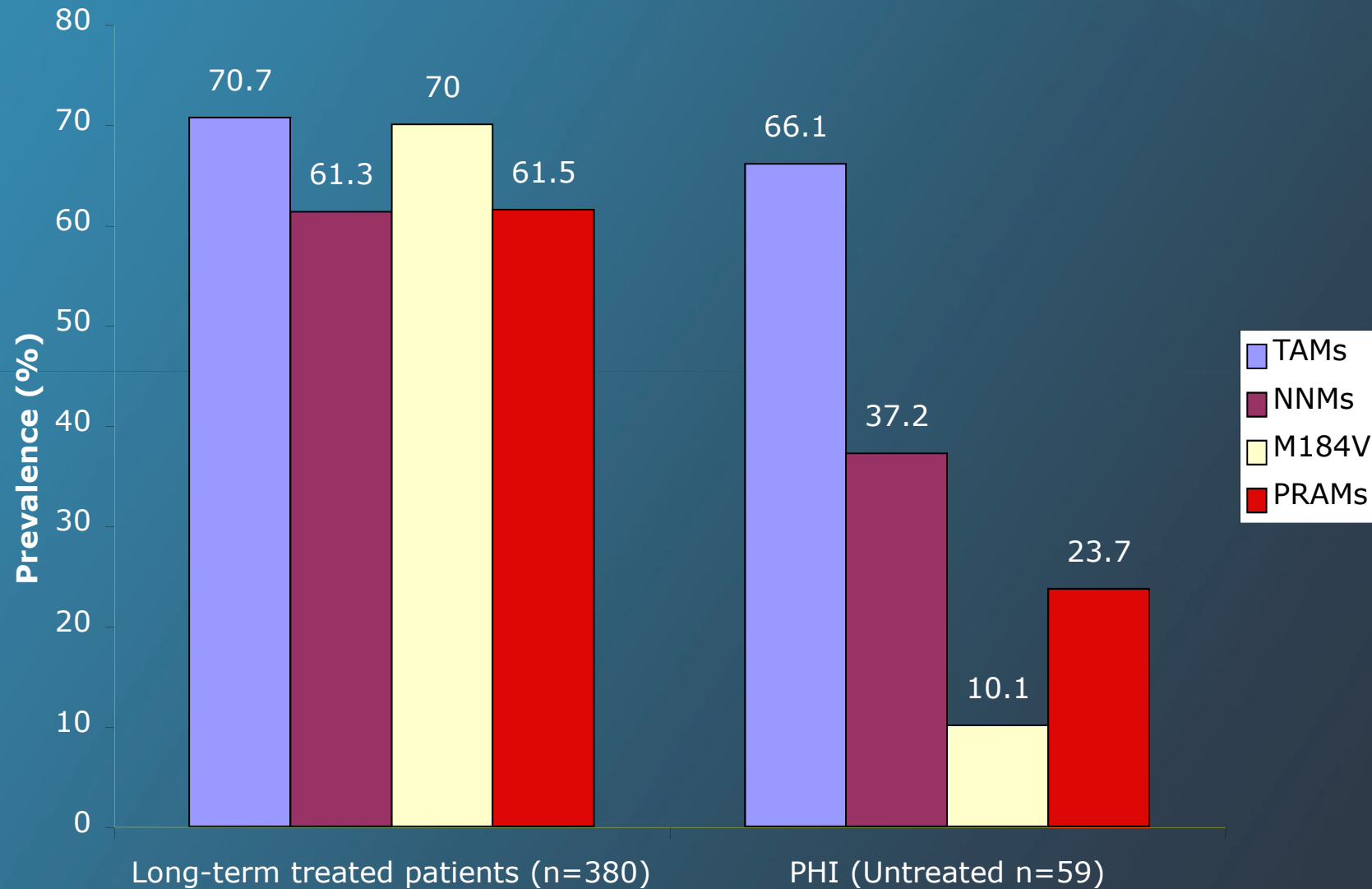


Figure 6. Time Trends for Transmitted Resistance Mutations by Geographic Region



## Differential Presence of Select Drug Resistance Mutations in Patient Populations



## Primary Antiretroviral Resistance in Brazil

Table 1. Studies on primary HIV-1 drug resistance conducted in Brazil.

Region of analysis	Period	Casuistic	Sample size	RT (%)		PR (%)	MDR <sup>a</sup> (%)	Total (%)
				NRTI	NNRTI			
Nationwide [4]	1996	Blood donors	32	0.9	0.0	N/A	N/A	0.9
Rio de Janeiro, RJ [5]	1998	Blood donors	49	0.0	0.0	0.0	0.0	0.0
Nationwide [7]	2001	Mixed	406	2.4	2.0	2.2	0.0	6.6
Rio de Janeiro, RJ [6]	2000–2002	Mixed	56	14.0	0.0	0.0	0.0	14.0

N/A, Not available; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PR, protease; RT, reverse transcriptase.

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**<sup>a</sup>MDR, Multi-drug resistant, defined as the presence of drug-resistant mutations for more than one class of antiretroviral drug.**

## Primary Antiretroviral Resistance in Brazil

	Recently acquired infection (%)	Long-standing infection (%)
NRTIs	22.7	21.1
T215Y/F	9.1	1.7
M184V	9.1	3.5
M41L	4.5	3.5
NNRTIs	0	15.7
PIs	13.6	8.1
Cumulative	32	29.2

M C A Sucupira. High Levels of Primary Antiretroviral Genotypic Resistance and B/F Recombinants in Santos SP, Brazil. 676, 11<sup>th</sup> CROI, San Francisco 2004.

## Prevalence of DR in HIV-Recently Infected and ARV Naive Persons in Latin America

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### Argentina

#### Recientemente infectados

– 4/52 (7.1%). 3 con K103N

J Acquir Immune Defic Syndr 2006;42:506

– 2/13 (15.4%), one with M46I and one M184V

Antivir Ther 2001;6:71

#### Polimorfismos poco usuales

– Codon 72 (AAG -AGG)

♦ 34% Argentina, 17% LA y 5% ROW

# Resistance in newly diagnosed never treated individuals in México

- **WHO supported study:**

DR prevalence in 11 testing and counseling centres in 9 states in Central Mexico

Genotypic data from 538 subjects:

- All but one (subtype F) sequences were HIV-1 subtype B.
- 40% had criteria for start treatment

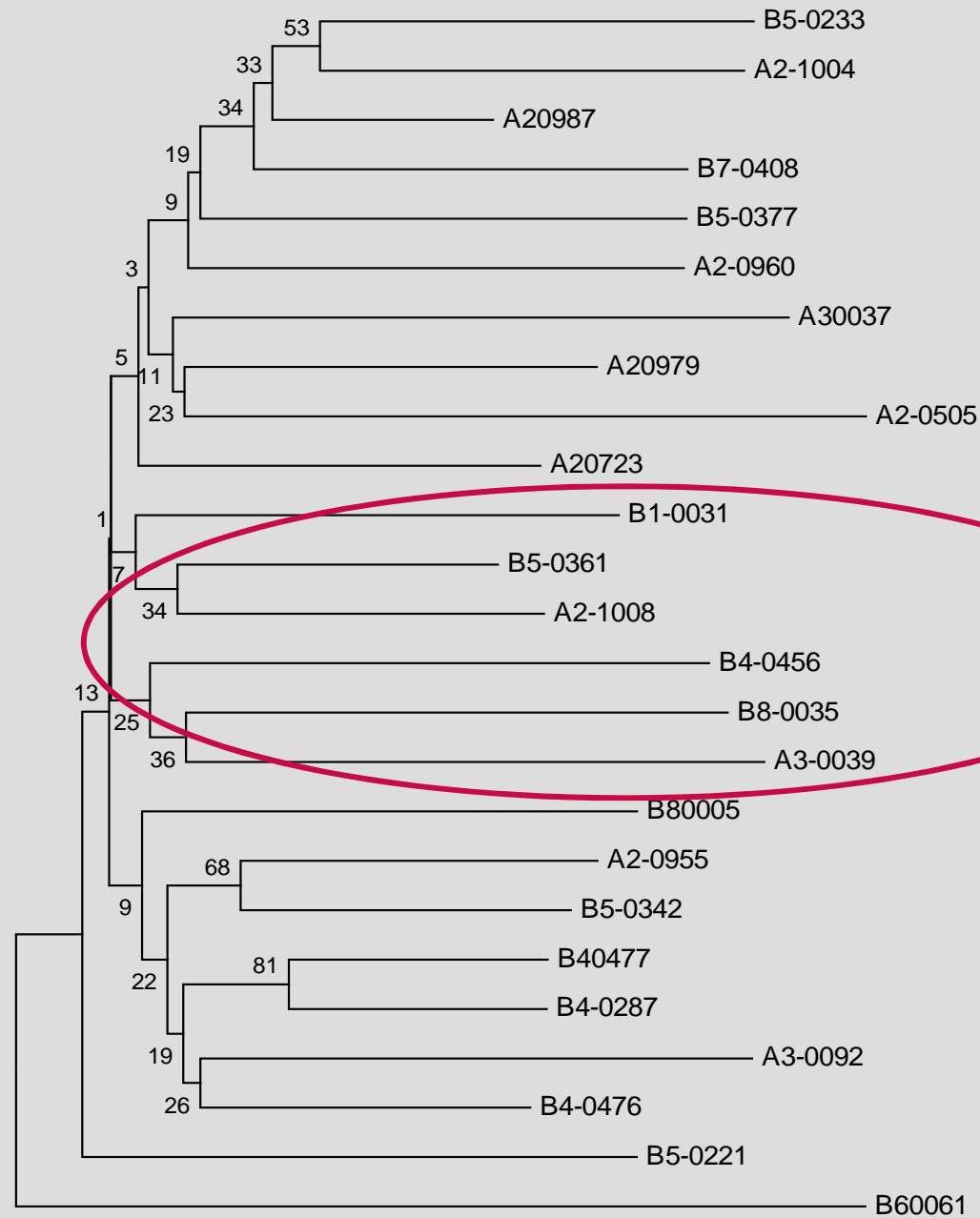
	Overall	NRTIs	NNRTIs	PIs	≥ 2 drug classes
Resistencia (Stanford)	7.2%	4.8%	2.7%	1.3%	1.8%
Mutations		M41L, T69N, V75I, L210 W, T215 C/D/N, K219Q	V106A, G190V	V82F	

- **En la frontera con California**

41 casos (10 recientemente infectados)

Solo un caso con resistencia (2.5%) con la mutacion K219Q

Soto-Ramirez et al. In Press AIDS Res Hum Retrovir  
Spector et all. [Int J STD AIDS. 2007; 18\(4\):235-8](#)



## HIV-1 transmission clusters from ARV naïve patients in Mexico

Our analyses demonstrate a cluster of transmission in Central Mexico with at least three possible events of transmission between individuals from the same city and from cities nearby. This transmission did not include resistant strains, maybe because of the low prevalence of transmitted resistance (7.4%). It is important to reinforce prevention policies in order to stop the dissemination of HIV infection in Central México

## Primary genotypic resistance in chronically infected patients screened for clinical trials in Mexico

	<b>n=193 (%)</b>
<b>Overall resistance</b>	<b>6 (3.1)</b>
Resistance to NRTI	4 (2)
Resistance to NNRTI	3 (1.5)
Resistance to PI	3 (1.5)
Resistance to 1 drug-class	3 (1.5)
Resistance to 2 drug-classes	2 (1)
Resistance to 3 drug-classes	1 (0.52)

	<b>NRTI</b>	<b>NNRTI</b>	<b>PI</b>
1		103N	
2	D67N, K219Q		M46I, I54V, V82A
3	M41L		M46I, I54V, V82A
4	67N, 74V, 115F, 151M, 215V, 219E	103N, 100I	54V
5	M41L, T215S		
6		103N	

■ Mutations conferring intermediate-resistance  
■ Mutations conferring high-resistance

## Prevalence of DR in HIV-infected ARV Naive Persons in Latin America

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### Venezuela

- 9.5% de 21 individuos

Poster C-18, XIII Congreso anamericano de Infectologia

- 10% en 20 individuos a nivel proviral

[AIDS Res Hum Retroviruses. 2007; 23\(3\):482-5](#)

### Chile

- 60 individuos en Santiago
- No resistencia transmitida

[Rev Med Chil. 2005; 133\(3\):295-301](#)

### Colombia

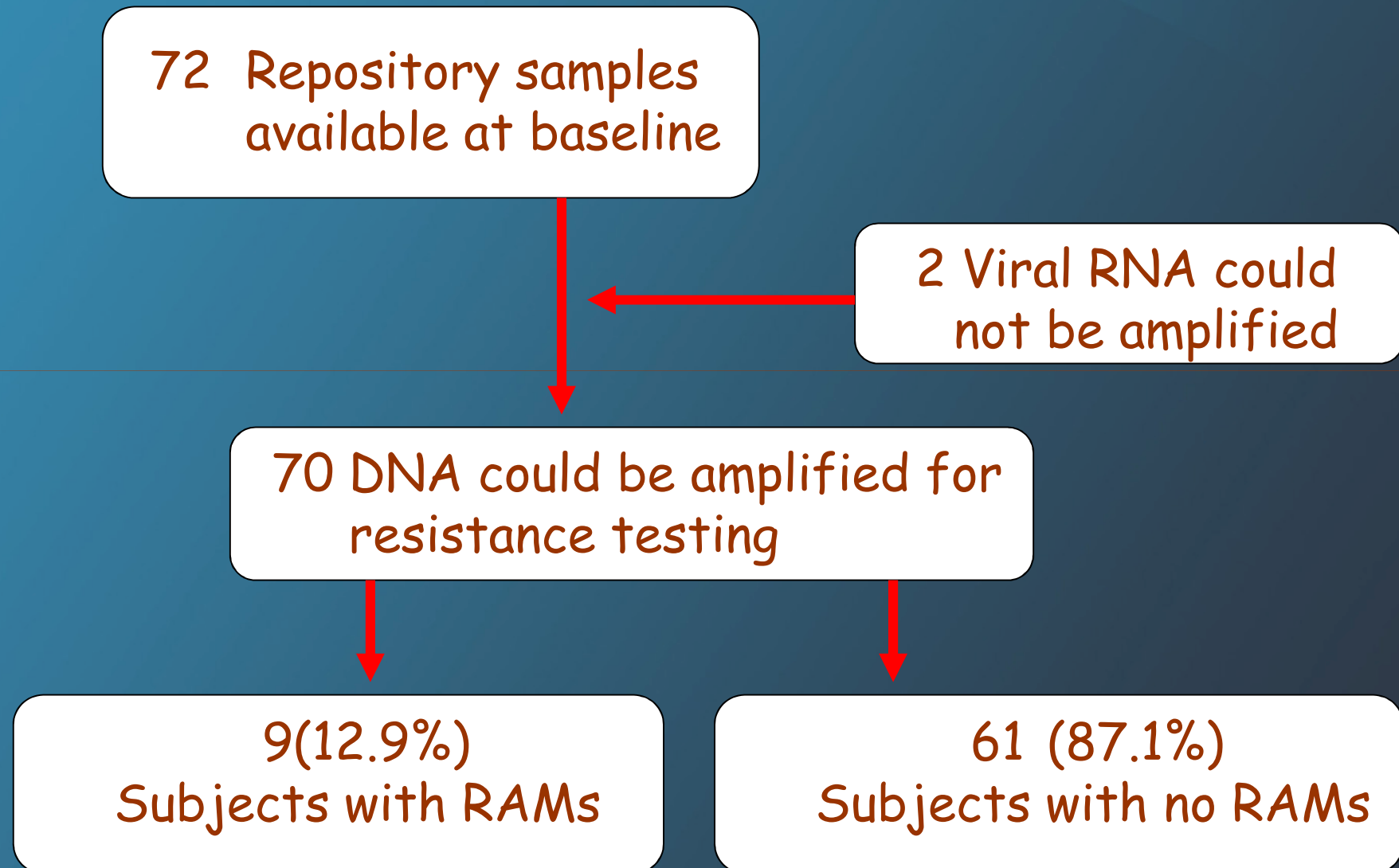
- 74 individuos
- 4% (K103N en todos y en uno coexistía con M184V)

### Cuba

- 27 individuos
- 7.4% a NRTIs and none to NNRTIs and PIs

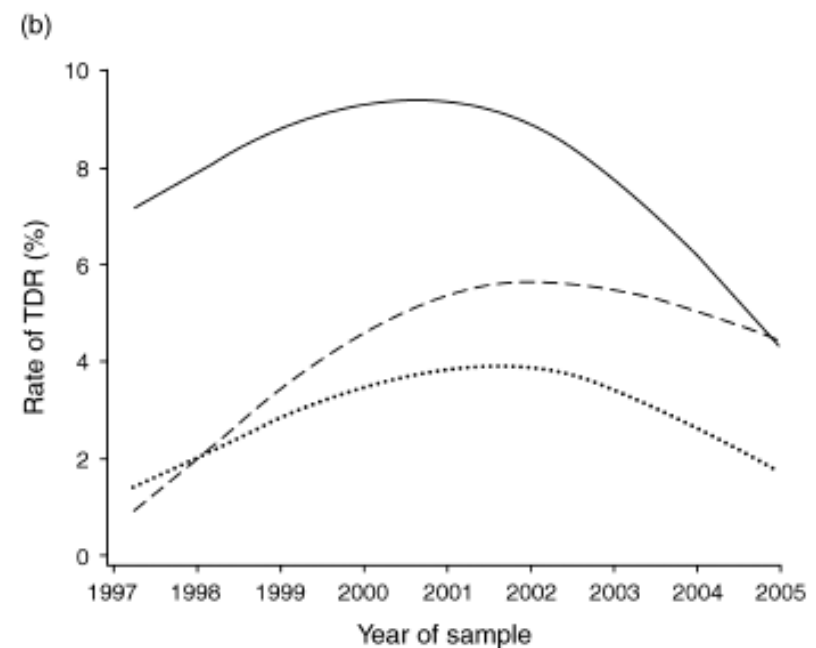
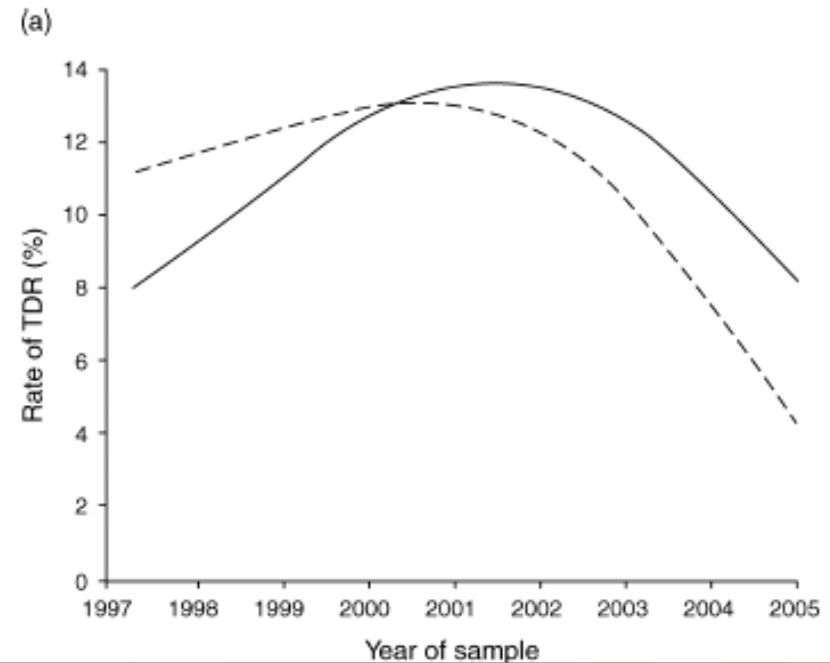
Rev Panam Salud Publica 2001;10:174

## HIV Drug Resistance in HIV-Infected Children Naive to ARV Treatment in Latin-American Countries



Disminución de resistencia transmitida en el Reino Unido

Disminuirá en LA???



# Impacto de la Resistencia Primaria

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- Preguntas relevantes

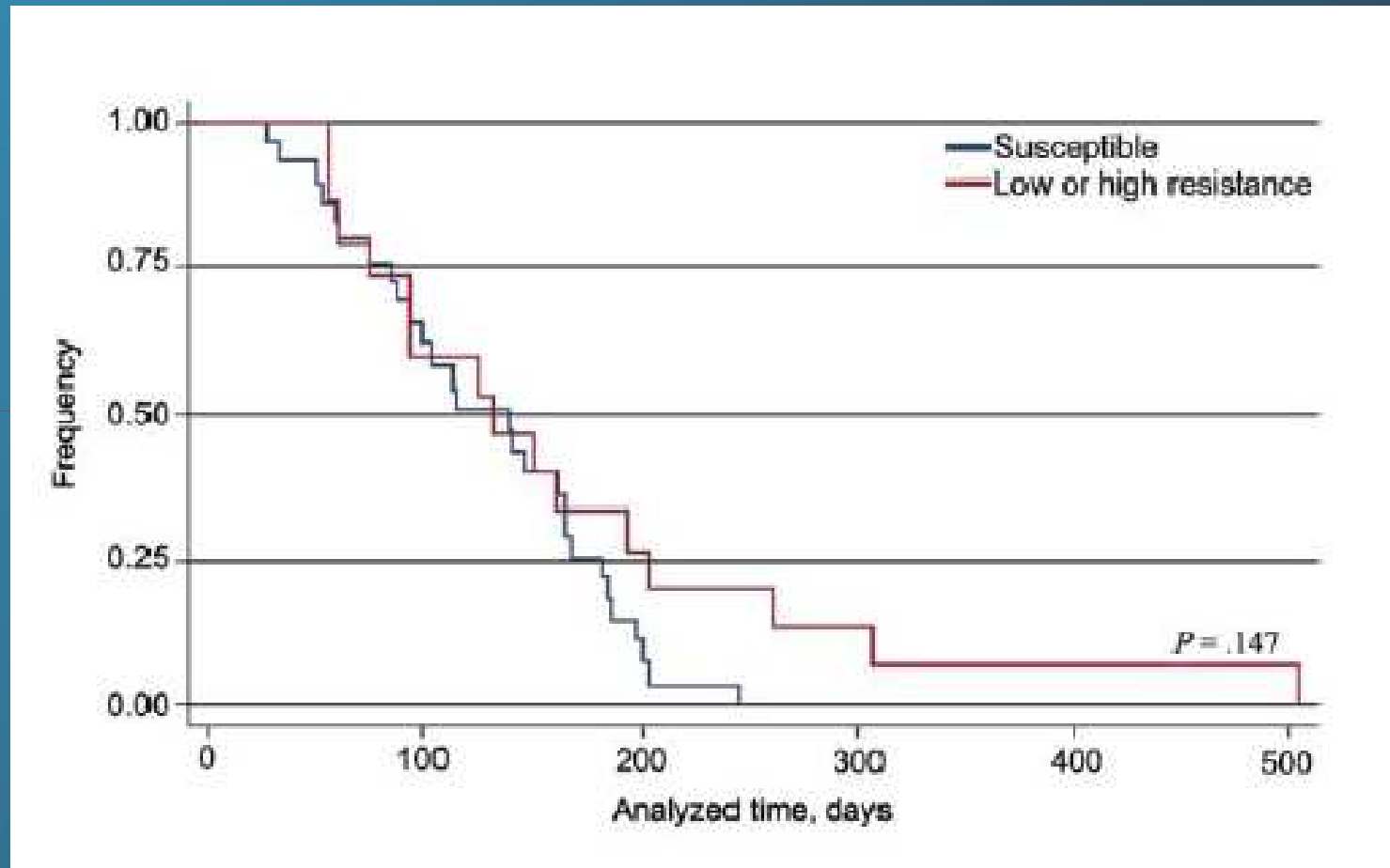
Pronóstico de pacientes que reciben cepas resistentes en el evento de transmisión

Impacto en el tratamiento antirretroviral

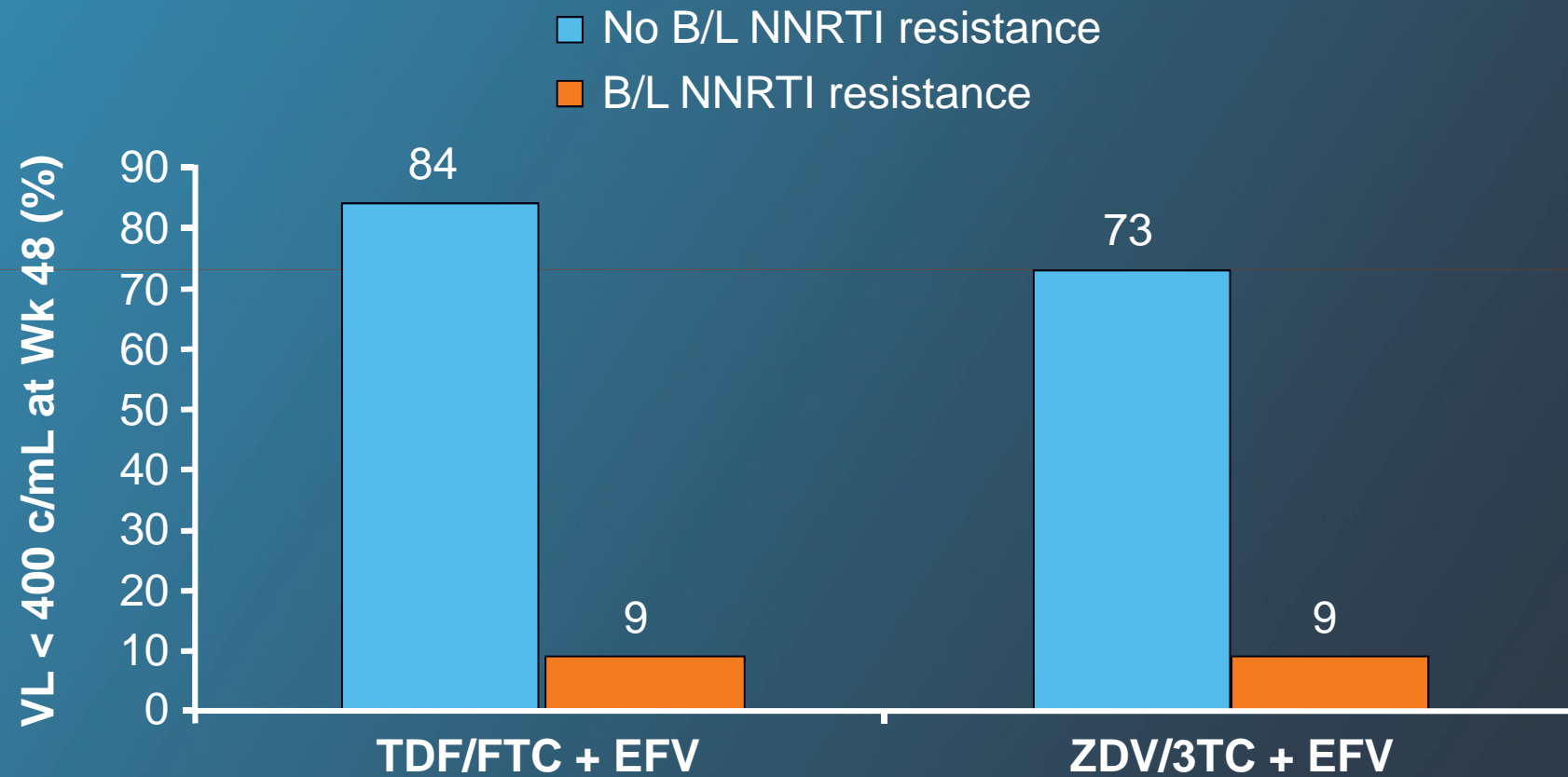
Uso de ensayos de resistencia antes de inicio de tratamiento

Cambio en las tendencias actuales del tx de inicio

## Efecto de la resistencia transmitida sobre el tiempo a supresión virológica



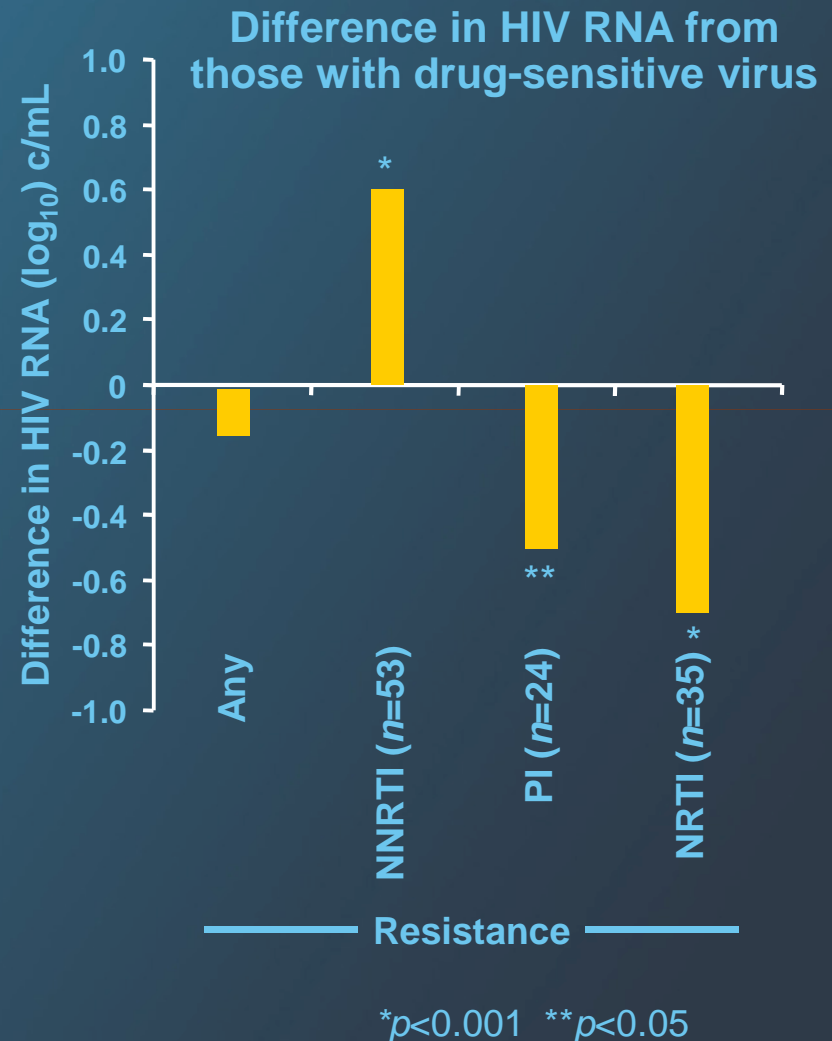
# GS934: Baseline NNRTI Resistance Markedly Reduces Virologic Response



## Resistance and steady-state HIV RNA in ART-naïve patients with primary infection

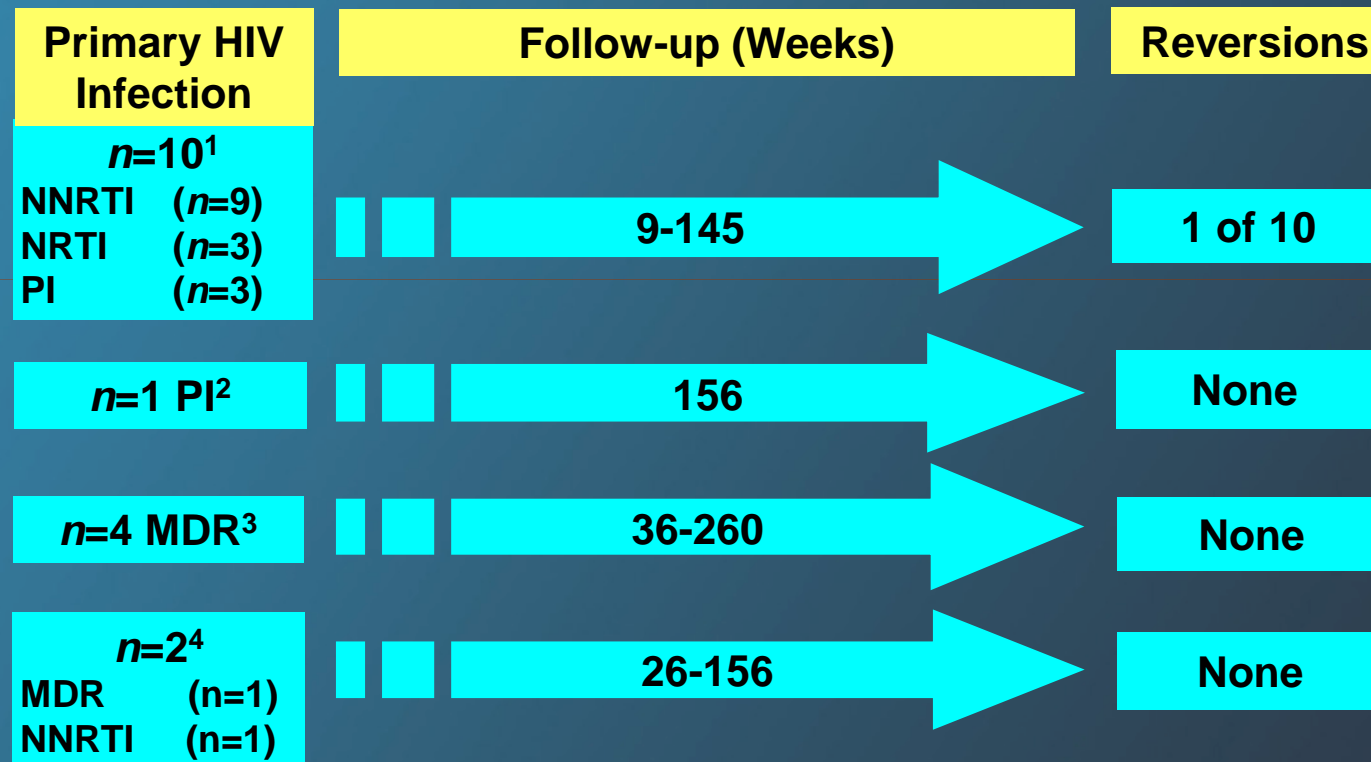
- Relationship between drug susceptibility and HIV RNA levels studied in patients with primary/recent infections (n=340)
- NNRTI resistance associated with increase in HIV RNA set point

No difference in replication capacity from wild type



## Persistence of transmitted resistant virus

- Reversion of DR is rare even after 1 year



1. Little SJ, *et al.* XII Resistance Workshop, Los Cabos 2003, #115; 2. Ravaux I, *et al.* 2<sup>nd</sup> IAS, Paris 2003, #822; 3. Brenner B, *et al.* J Virology 2002; 766:1753; 4. Chan K, *et al.* AIDS 2003; 17:1256

# Genetic Barrier and Transmitted Resistance

Mutations  
required for  
resistance

## Impact of single transmitted mutation



Boosted PI

NNRTI

Activity:

Retained

Lost

Remaining GB:

Substantial

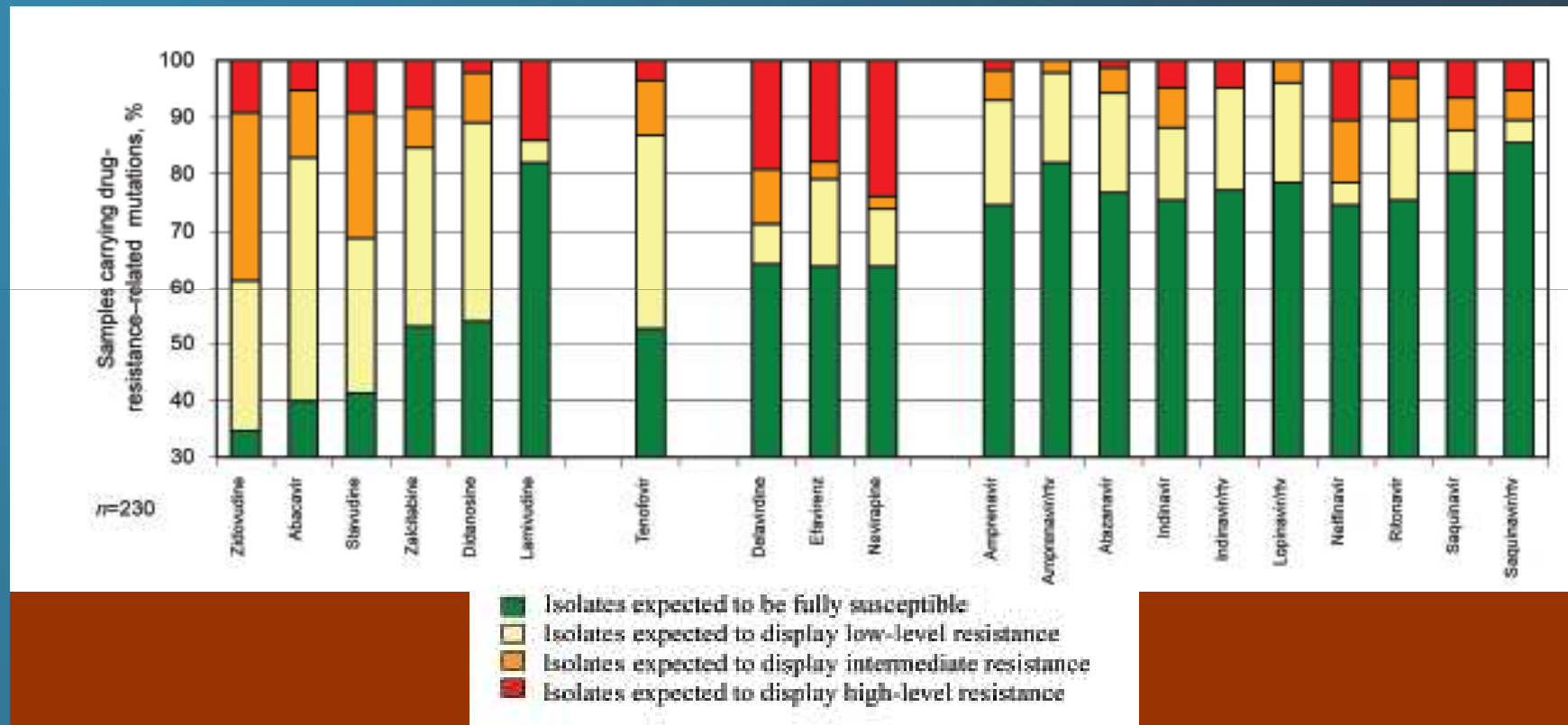
None

Protection of other drugs in  
regimen:

Mostly Retained

Lost

# Predicted Susceptibility of Transmitted Resistance in Recently Infected Patients (1996-2002)



# Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance

PI		NRTI		NNRTI	
L24	I	M41	L	L100	I
D30	N	K65	R	K101	E
V32	I	D67	N, G, del	K103	N, S
M46	I	T69	D, ins	V106	A, M
I47	V, A	K70	R	Y181	C, I
G48	V	L74	V	Y188	L, H, C
I50	V, L	V75	T, M, A, S	G190	A, S, E, Q
F53	L	F77	L	P225	H
I54	V, M, L, T, S, A	Y115	F	M230	L
G73	S, T, C, A	F116	Y	P236	L
V82	A, T, F, S, M	Q151	M		
I84	V, A, C	M184	V, I		
N88	D, S	L210	W		
L90	M	T215	Y, F, X		
		K219	Q, E, R		

## Numbers of HIV-1 Protease and RT Sequences from untreated individuals in the Stanford Database eligible for this analysis, by HIV-1 Subtype

HIV-1 Subtype	Protease sequences from PI-Naive Persons*	RT sequences RTI-naïve Persons*
<i>Subtype B</i>		
<b>B</b>	<b>3,439</b>	<b>2,120</b>
<i>Non-B subtypes</i>		
<b>A</b>	<b>642</b>	<b>477</b>
<b>AE</b>	<b>673</b>	<b>604</b>
<b>AG</b>	<b>795</b>	<b>470</b>
<b>C</b>	<b>1006</b>	<b>895</b>
<b>D</b>	<b>335</b>	<b>166</b>
<b>F</b>	<b>171</b>	<b>125</b>
<b>G</b>	<b>264</b>	<b>137</b>
<b>NonB total</b>	<b>3,886</b>	<b>2,874</b>

## Caso: EC-JF

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- JF es un hombre de 34 años quien fue atendido hace 4 años por un síndrome retroviral agudo
- Se realizó un genotipo de resistencia:
  - Transcriptasa reversa: 41L, 103N, 215Y
  - Proteasa: 77, 82A, 90M
- En su última visita hace 2 semanas presenta los siguientes resultados:

Un conteo de células CD4+ (275 cel/mm<sup>3</sup>) y CV 145,000 copias/ml
- Se volvió a realizar un genotipo que no mostró otras mutaciones.
- Con que le iniciarían tratamiento?

## Caso: ASJ

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- ASJ es un hombre de 38 años quien acude con su pareja por haber salido positivo a un ELISA/WB el 5 de Enero con CV > 750,000 copias/ml y un genotipo de resistencia con:
  - K70R, T215Y, K219Q, G190S y Y181C
- Pareja: RMW, masculino de 23 años infectado hace 4 años con CD4s mayores a 500 y CV menores de 20,000 copias/ml. Sin tratamiento ARV.
- Desde que se enteraron de la positividad de RMW han sido fieles aunque no siempre se protegen.
- El día 7 de febrero se realizaron:
  - RMW: genotipo: Sin mutaciones asociadas a resistencia
  - ASJ: CD4s 358 (18%), CV 496,000 copias/ml. y un genotipo que no mostró mutaciones.
- Que harían?



# LA HIV ResNet



**Latin American HIV  
Resistance Network**

**Bogotá, Colombia  
Mayo 6, 2010**