13:50 – 14:20

MINI CONFERÊNCIA: A RESISTÊNCIA TRANSMITIDA (HIV) NO BRASIL

Coordenadora/Debatedora: Lucy Cavalcanti Ramos Vasconcelos

13:50 – 14:00 Conferencista: Marcos Montani Caseiro

14:00 – 14:10

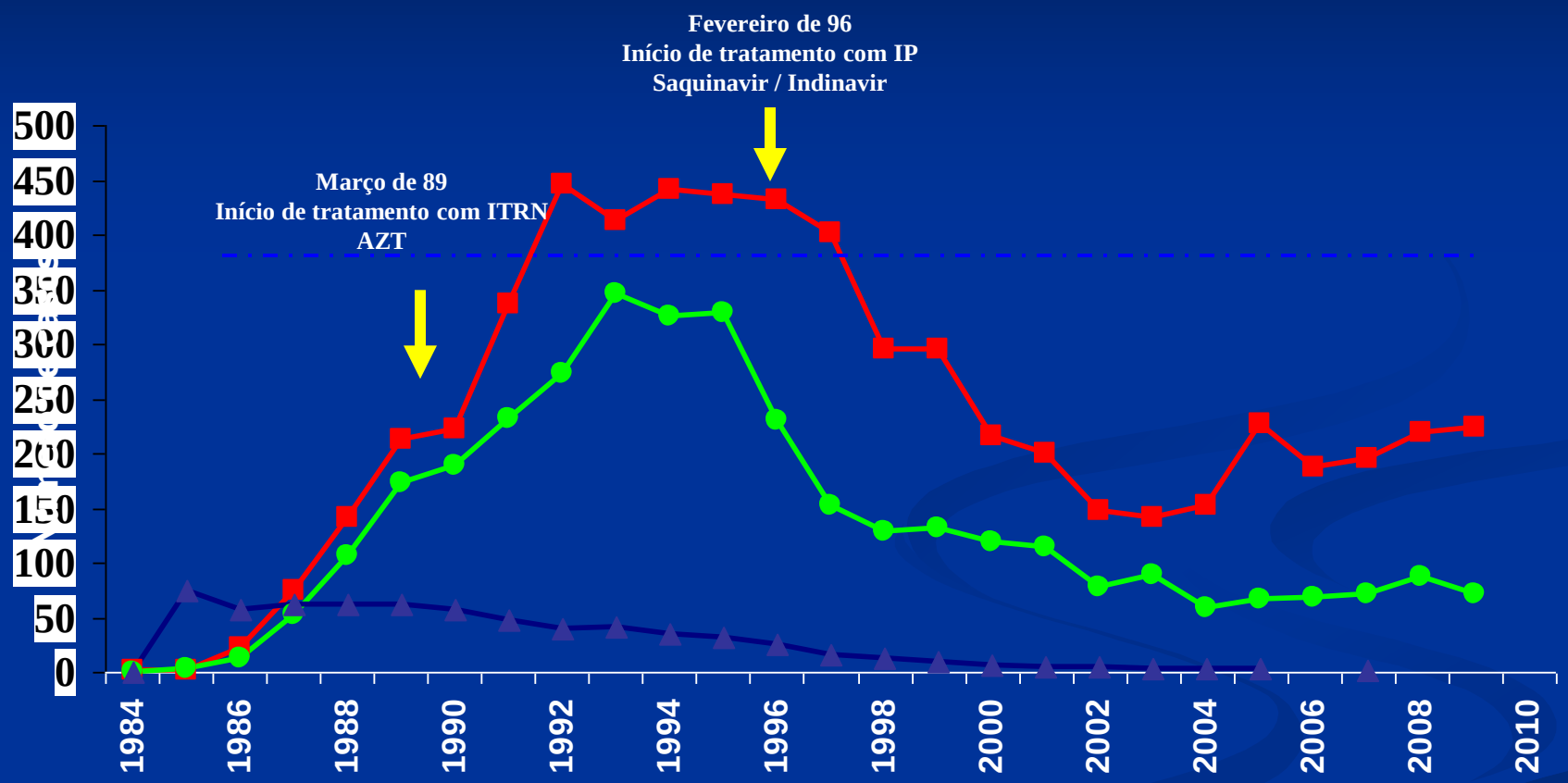
Apresentação de Caso Clínico

Alexandre Naime Barbosa

14:10 – 14:20 Discussão

Marcos Montani Caseiro, MD, PhD
Lusíada Foundation, Associate Professor
Bolsista CNPq- Produtividade em Pesquisa 2
Molecular Biology Lab

Número de casos de Aids, óbitos, letalidade e uso de IP no município de Santos – 1984 - 2010.

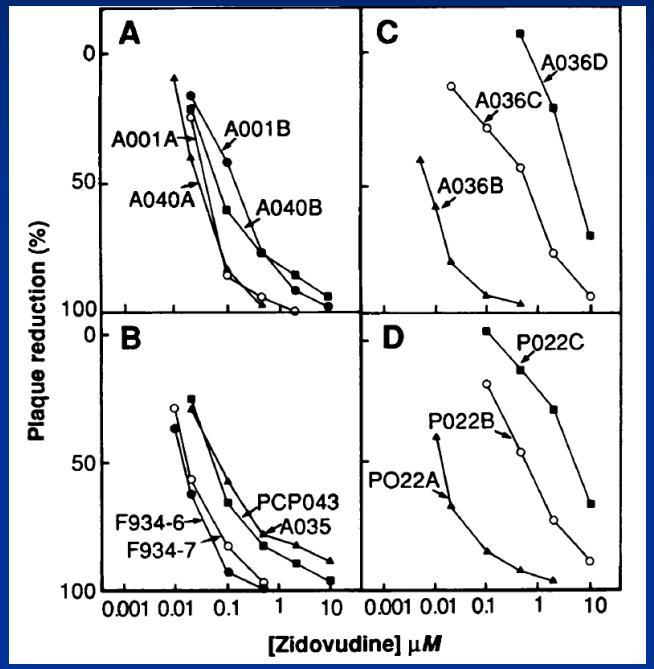


	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Casos	2	2	23	74	142	213	222	337	446	412	442	436	431	402	295	295	216	200	148	141	152	227	188	196	219	224	
Óbitos	0	3	13	53	107	173	189	231	273	346	325	329	230	153	128	132	119	115	78	89	59	67	68	72	88	72	
Letalidade	0	75	56,5	61,9	61,7	62,5	57,9	48,4	39,9	41,6	35,2	31,7	25,3	15,5	12,1	9,9	6,8	5,1	4,1	2,8	2,4	2,7		1,9			

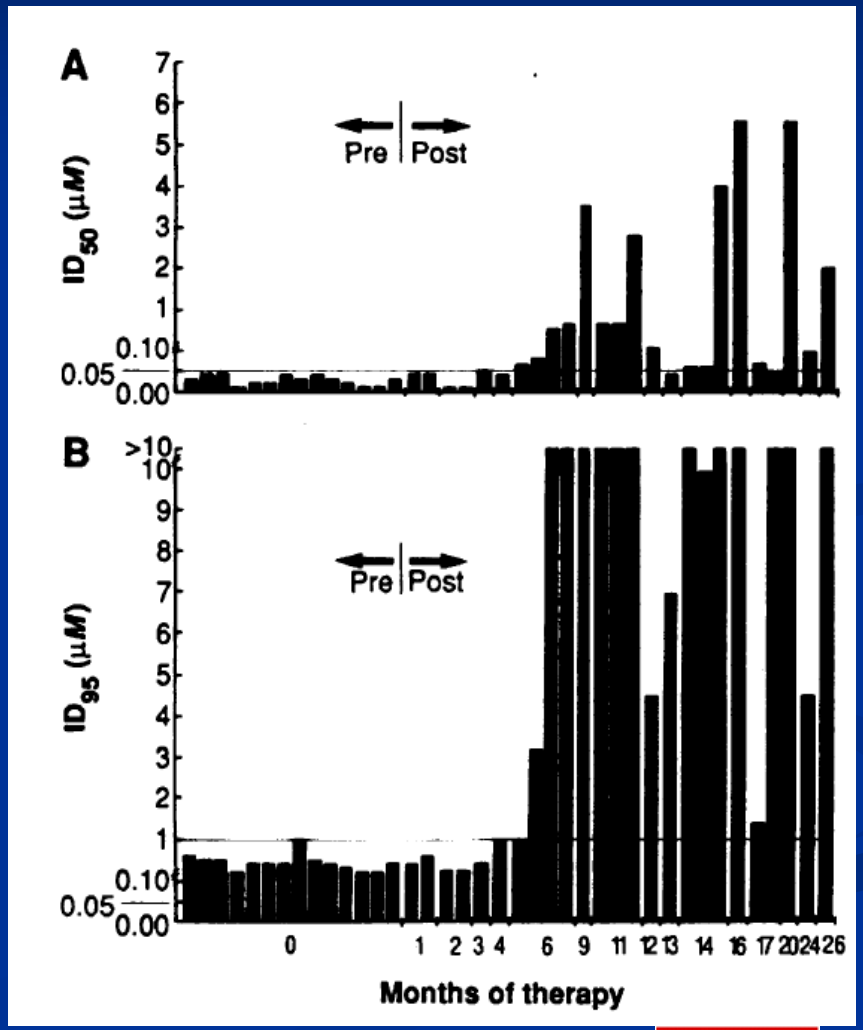
Fonte: Boletim Epidemiológico do Município de Santos
Dados incompletos até 30/12/2010.

HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy

BRENDAN A. LARDER, GRAHAM DARBY, DOUGLAS D. RICHMAN



Duration of therapy (months)	Number of isolates	ID_{50}		
		Mean (μM)	Median (μM)	Range (μM)
None	18	0.03	0.03	0.01–0.05
1–5	6	0.03	0.03	0.007–0.05
6–11	8	1	0.6	0.06–4
12–17	8	1	0.07	0.04–6
18+	3*	3	2	0.1–6



Science
AAAS | 31 MARCH 1989

Conceitos e Definições

- **Resistência transmitida** – detectada em pacientes virgens de tratamento anti-retroviral
- **Resistência secundária** – decorrente da pressão seletiva exercida pelas drogas
- **Resistência a múltiplas drogas (MDR)** – as mutações conferem resistência a todas as drogas de uma classe.

Mecanismos de Resistência

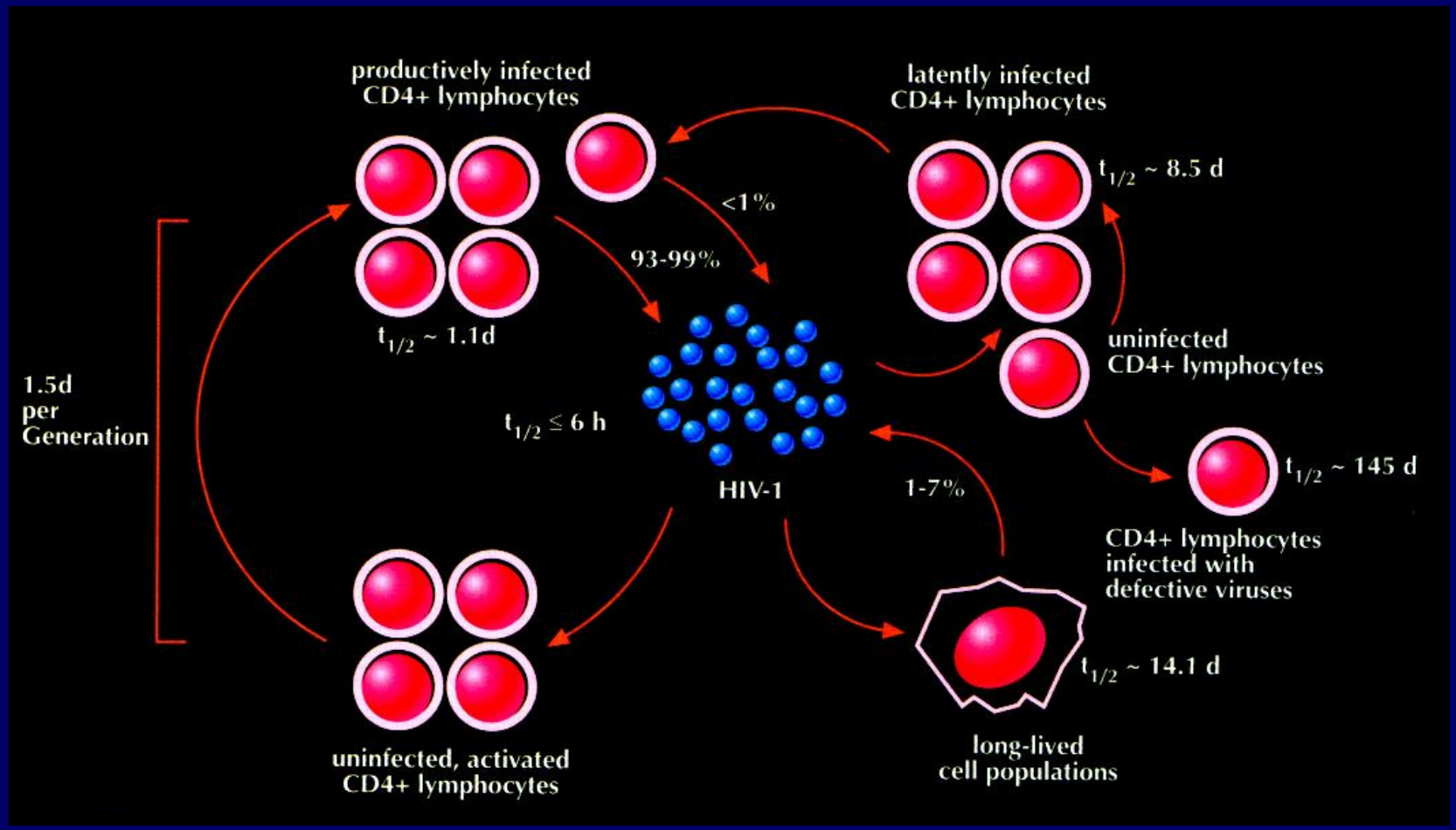
A seleção de mutações ocorre facilmente devido às características do ciclo de vida do HIV:

- Alto índice de erros naturais da transcriptase reversa
- Alto índice de replicação viral
- **Elevado número de ciclos replicativos (> 300 ciclos/ano)**
- Tamanho do genoma do HIV **(RNA) de ~10^4 nucleotídeos**

=> essa diversidade genética é responsável pelo sucesso do vírus

Todas as possibilidades de mutações são geradas a cada dia no genoma viral...

Dinâmica Viral

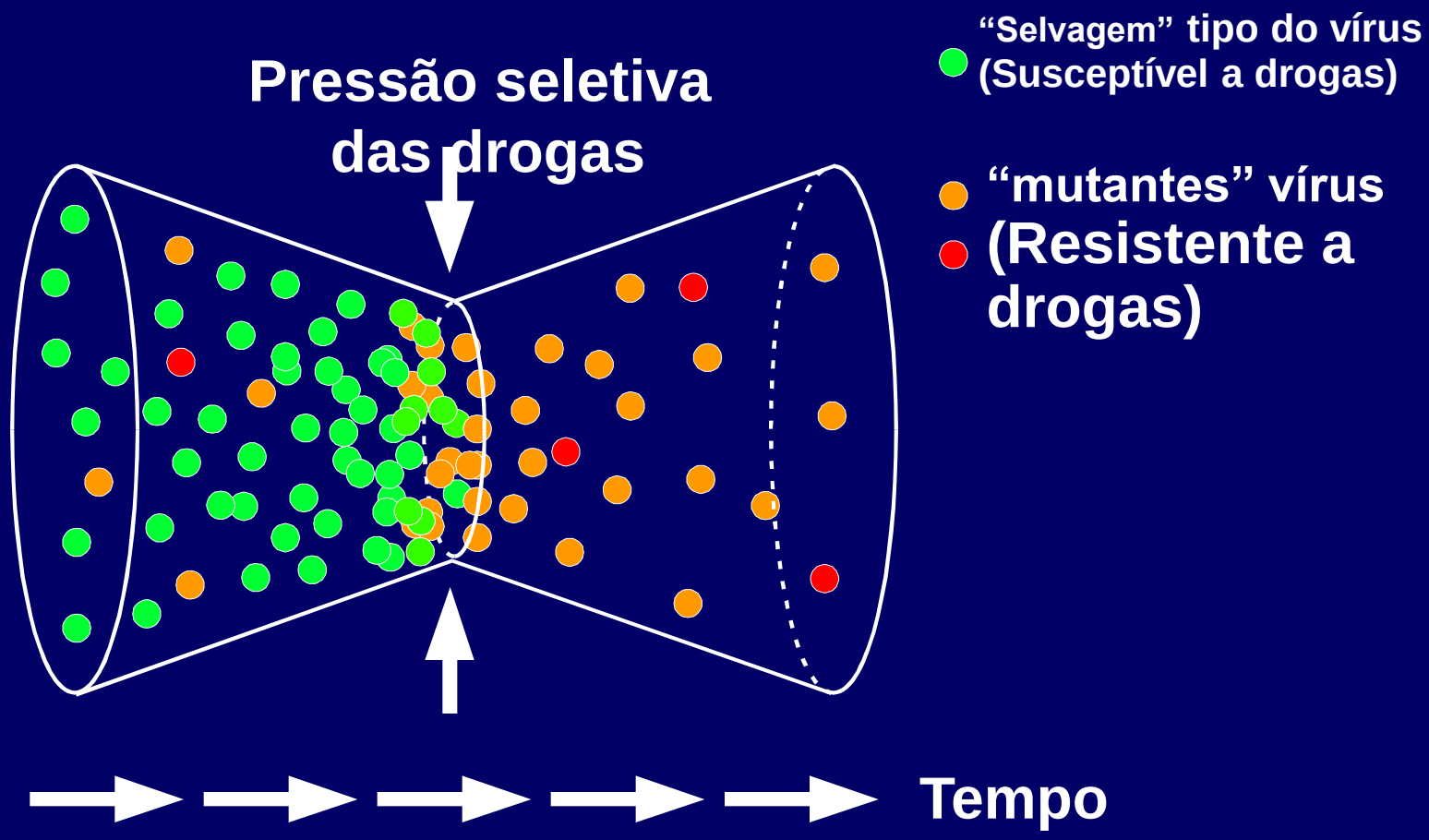


Mecanismos de Resistência

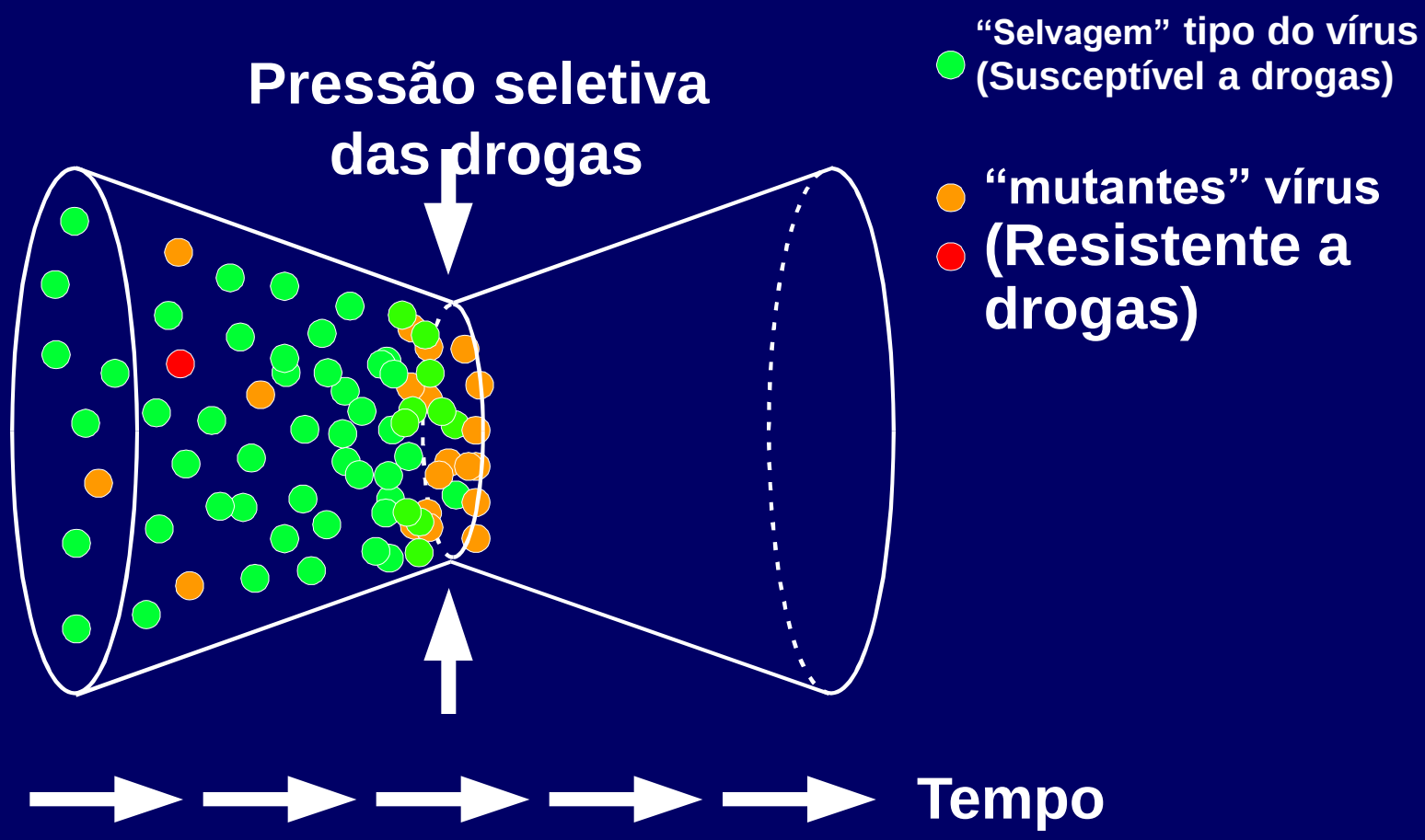
- Por outro lado, essas mutações não se fixam porque a cepa viral mutante tem que competir com o vírus selvagem que se encontra em maior número

- A fixação e a posterior infecção de novos linfócitos ocorrerão quando for utilizado um regime anti-retroviral não supressivo, eliminando os vírus sensíveis e "selecionando" mutantes, que irão se replicar

Dinâmica Viral e Resistência a drogas

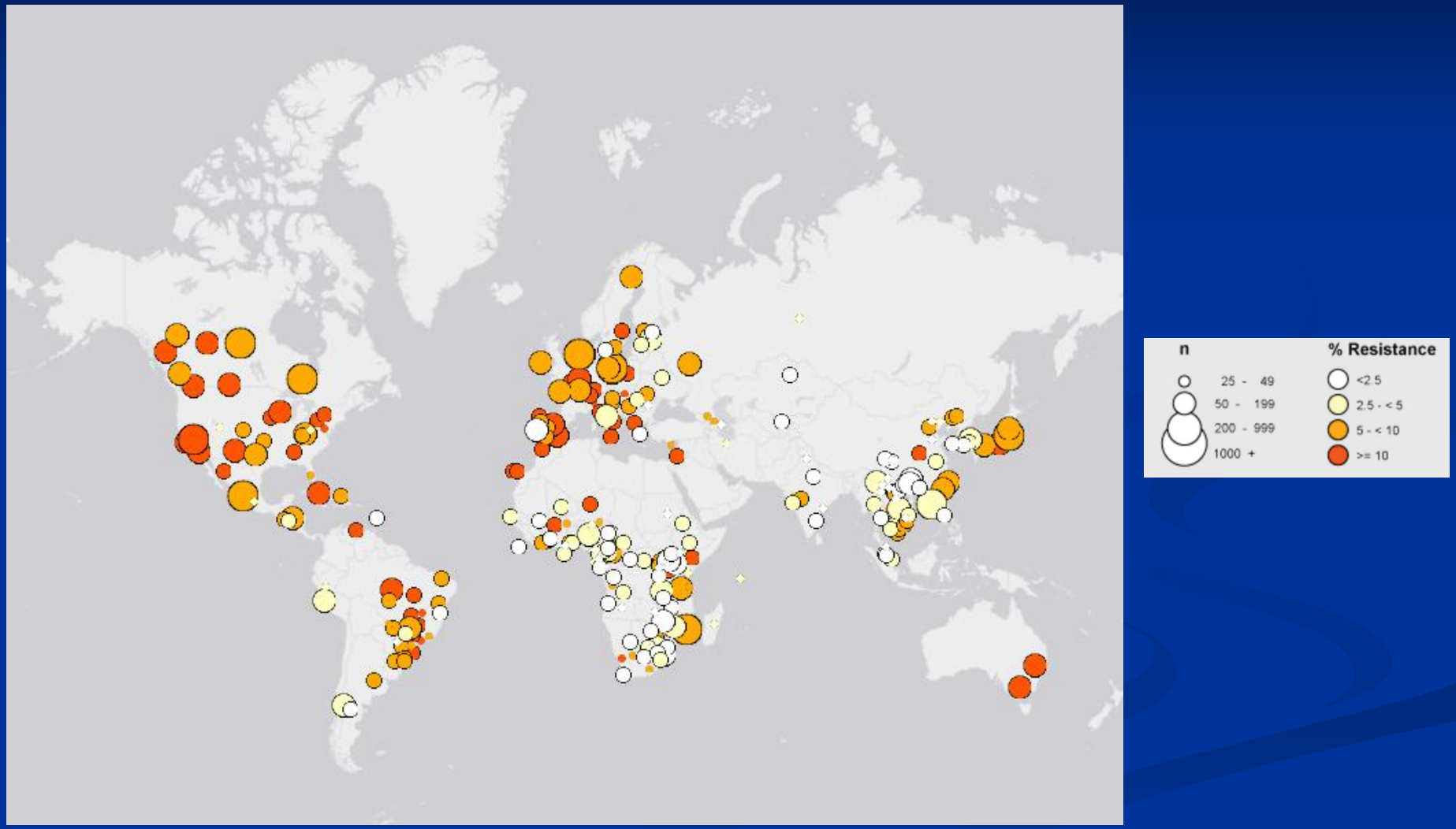


Dinâmica Viral e Resistência a drogas
(O ideal !!)



Resistência no mundo

(Alguns dados)



http://hivdb.stanford.edu/surveillance/map/

Resistência no mundo

(Alguns dados)

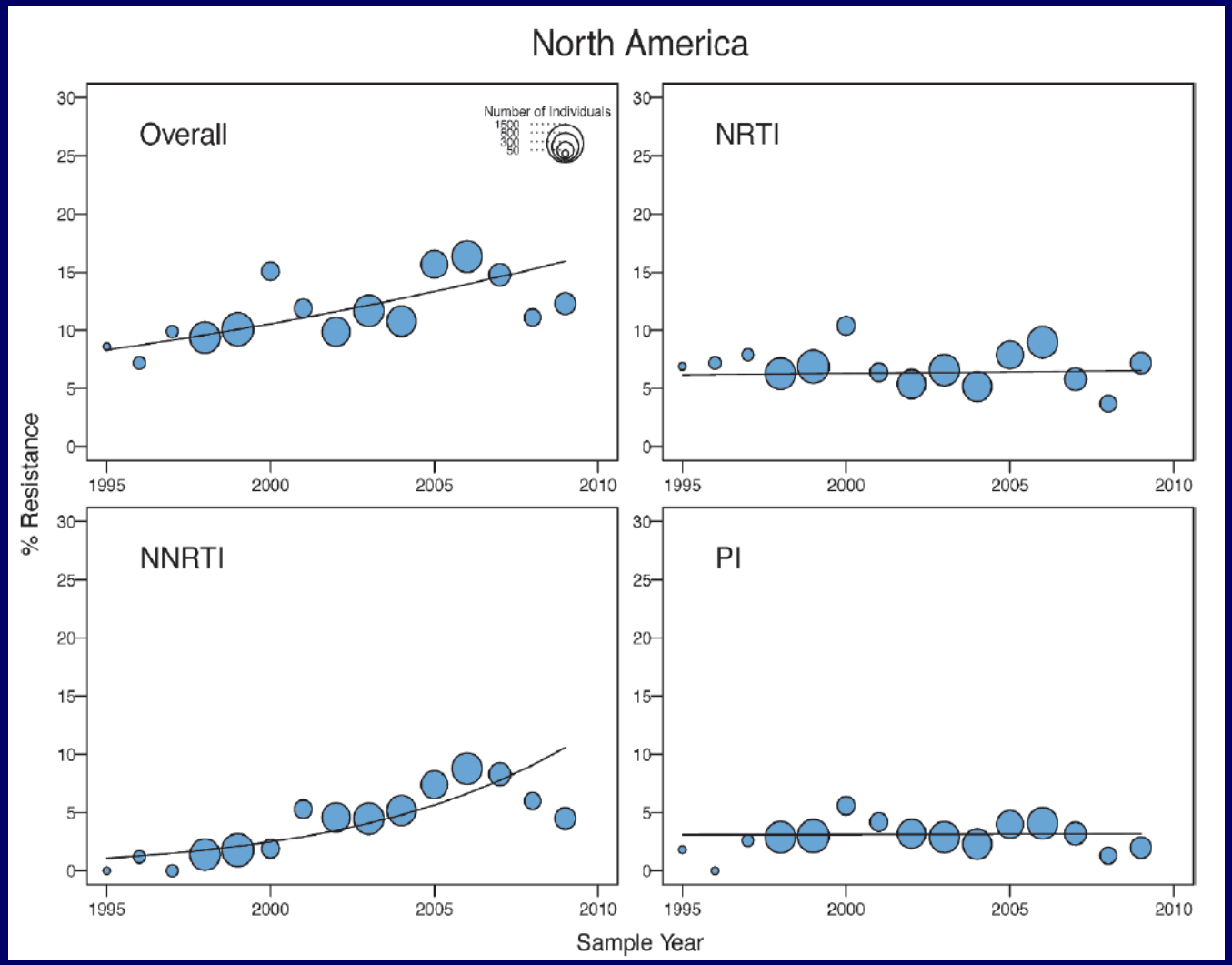
Estimativa Média da Resistencia transmitida em sete regiões Geoeconômicas

TDR	SSA (*n* = 95)	SSEA (*n* = 56)	Latin America/ Caribbean (*n* = 38)	Europe (*n* = 42)	North America (*n* = 27)	Upper-Income Asia (*n* = 12)	FSU (*n* = 12)
Overall	2.8% (1.3%–5.6%)	2.9% (1.8%–5.3%	7.6% (3.9%–10.2%)	9.4% (6.1%–15.1%)	11.5% (8.3%–14.6%)	5.6% (3.5%–9.0%)	4.0% (0%–6.4%)
NRTI	0% (0%–2.4%)	1% (0%–2.4%)	4% (1.8%–6.6%)	5.6% (3.1%–10.1%)	5.8% (3.4%–8.2%)	3.5% (1.5%–5.0%)	1.8% (0%–3.9%)
NNRTI	1.4% (0%–2.8%)	0.8% (0%–2.1%)	2.8% (1.1%–5.0%)	3.4% (1.5%–5.3%)	4.5% (3.0%–6.8%)	1.1% (0.2%–1.6%)	0.8% (0%–2.1%)
PI	0% (0%–1.4%)	0.5% (0%–1.9%)	1.4% (0%–3.0%)	1.5% (0%–2.8%)	3.0% (2.3%–3.9%)	1.6% (0.6%–3.0%)	0.2% (0%–2.1%)

PLOS Medicine | DOI:10.1371/journal.pmed.1001810 April 7, 2015

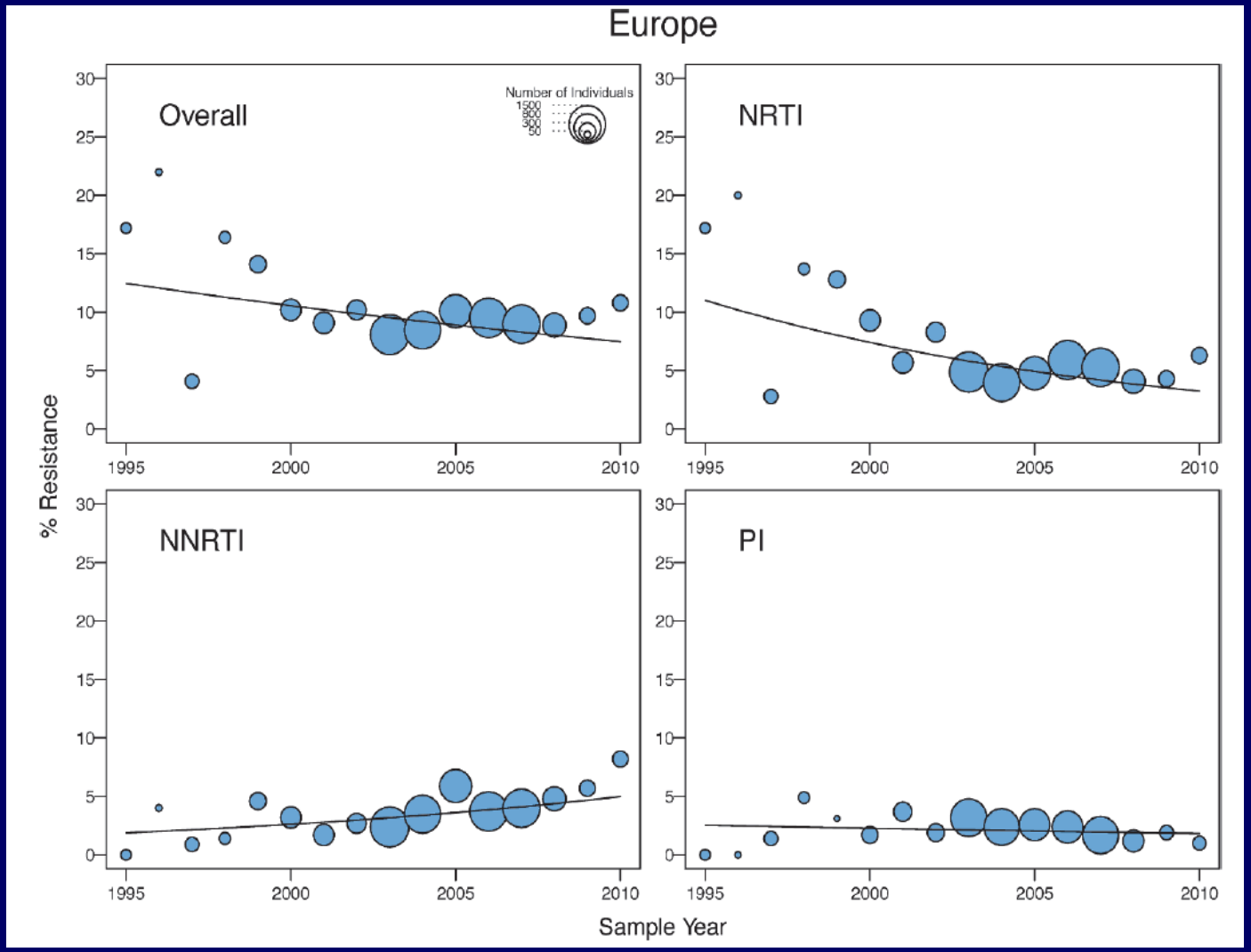
Resistência no mundo

(América do Norte)



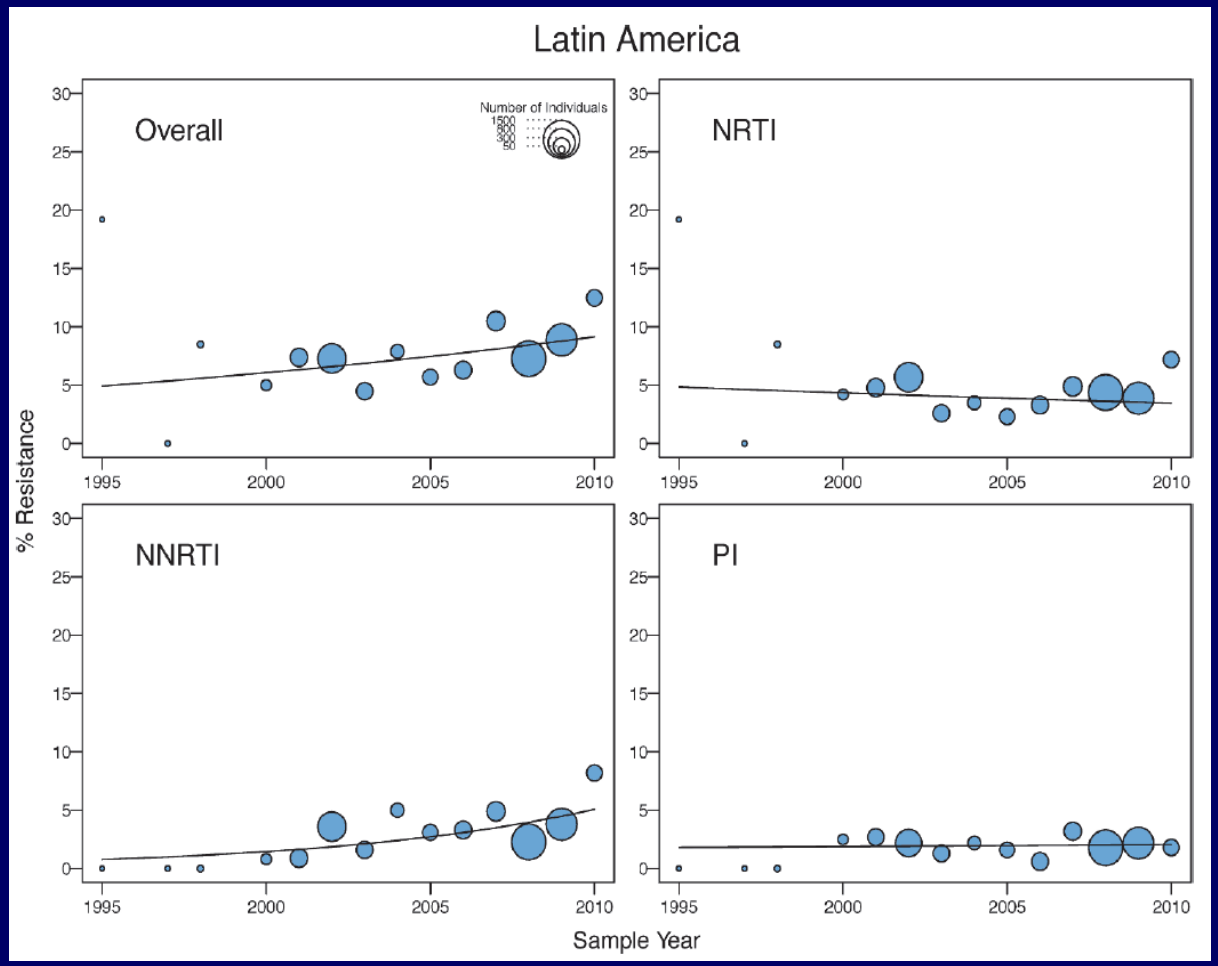
Resistência no mundo

(Europa)



Resistência no mundo

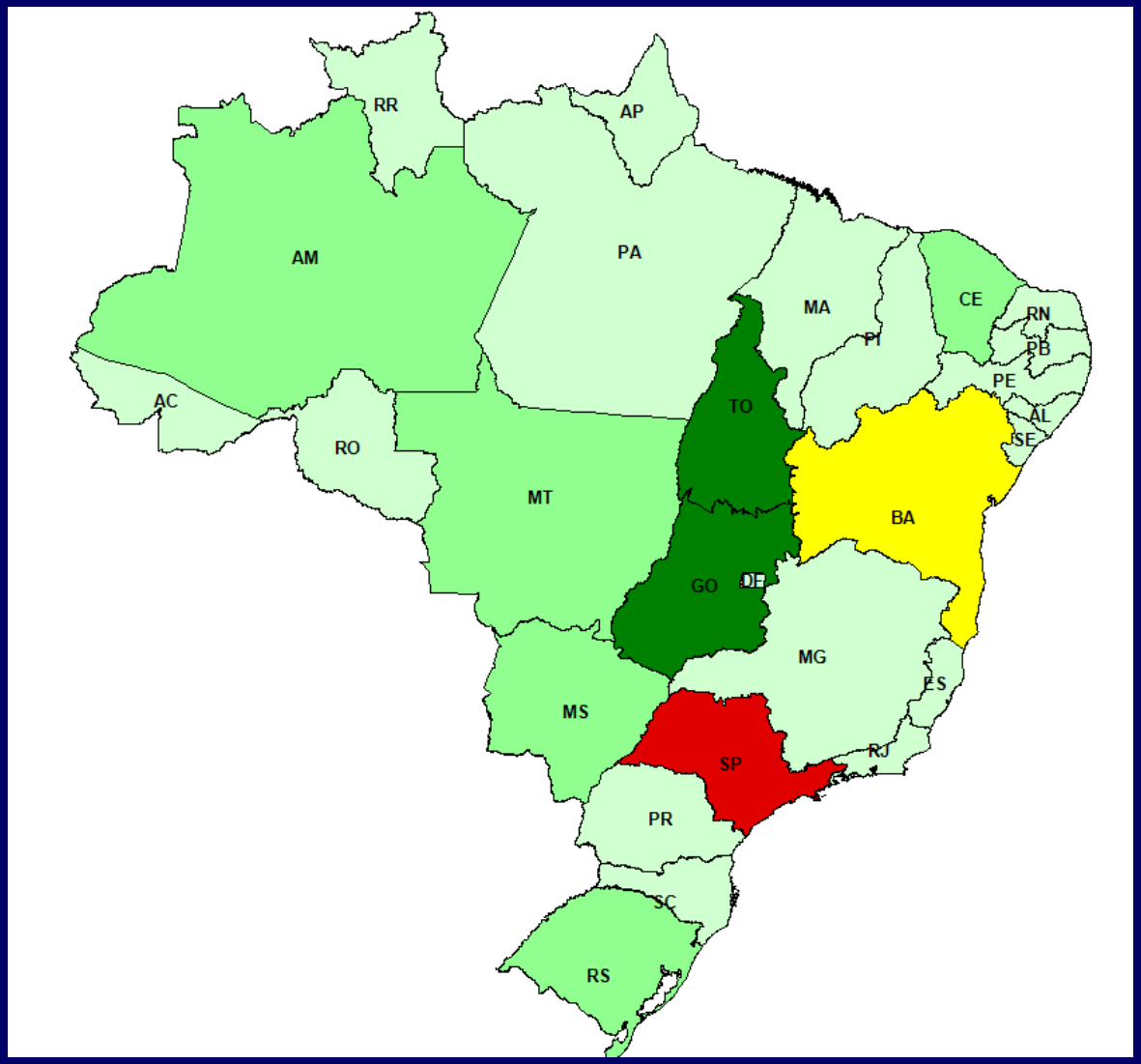
(América Latina)



Resistência no Brasil

PUBLICAÇÃO	AUTOR		ESTADO	ANO	n	POP	FONTE	RES_TOTAL	ITRN	ITRNN	IP
AIDSPCSTDS	SUCUPIRA, CASEIRO 07	Santos	SP	1996-1999	68		PLASMA	22,7	22,7	15,7	13,6
AAC	DUMANS 02		RJ	1998	47	BD	PLASMA	8,5	8,5	0	0
J MED VIROL	VARELLA 07		RJ	2000	50	HIVC	PLASMA	0	0	0	0
J MED VIROL	MAIA TEIXEIRA 06		RJ	2000	65	IVUD	PBMC	15,4	17,6	2	4,6
AIDS	SOARES 03		RS	2001	93	VCT	PLASMA	6,5	3,2	2,2	2,6
AIDS	BRINDEIRO 03	HIV-BResNet	HIV-BResNet	2001	190	VCT	PLASMA	9,5	6,6	0,5	3,8
J CLIN MICROBIOL	PIRES 04	Exercito	RJ	2002	49	HIVC	PLASMA	10,2	10,2	0	0
ARHR	GAGLIANI, CASEIRO 11	Santos	SP	2002	79	HIVC	PLASMA	33,7	20	16,2	2
VIRUS RES	RODRIGUES 06	Porto Alegre	RS	2004	96	VCT	PLASMA	5,2	2,2	3,2	0
PLoS ONE	SANABANI 11		SP	2004	50	HIVC	PBMC	10	4	4	4
VIRUS RES	GONSALEZ 07		SP	2005	105	HIVC	PLASMA	2,9	1	1,9	1
MEM INS O CRUZ	FERREIRA 08	Curitiba	PR	2006	49	VCT	PLASMA	6,1	2	4,1	0
J MED VIROL	de MEDEIROS 11	Porto Alegre	RS	2006	99	HIVC	PBMC	7,1	2	3	2
ARHR	BRIGIDO 07		SP	2006	195	HIVC	PLASMA	9,7	6,7	6,7	1,8
J CLIN VIROL	SANTOS 11		RS	2007	87	HIVC	PLASMA	9,2	4,7	4,7	3,3
J CLIN VIROL	CARDOSO 09	Goiania	GO	2007	97	HIVC	PLASMA	10,3	6,3	4,2	3,1
ARHR	CASEIRO, SA-FILHO 09	Santos	SP	2007	30	HIVC	PBMC	23,3	10	13,3	3,8
ARHR	da SILVEIRA 12	Campo Grande	MS	2008	49	HIVC	PLASMA	6,1	6,1		
J MED VIROL	FERREIRA 11	Cuiabá	MT	2008	92	HIVC	PLASMA	6,5	4,5	1,1	1,1
ARHR	ARRUDA 10	Fortaleza	CE	2008	74	HIVC	PLASMA	9,5	4,1	2,7	4,1
ARHR	CARVALHO 11	Palmas	TO	2008	52	HIVC	PLASMA	11,5	3,9	5,9	1,9
J CLIN VIROL	GRAF 11	Florianópolis	SC	2008	82	HIVC	PBMC	12,2	7,3	3,7	3,7
RIMTSP	GASPARETO 12	Maringá	PR	2009	48	HIVC	PLASMA	2,1	0	0	2,1
ADV VIROL	FERREIRA 13		SP	2009	224	HIVC, VCT	PLASMA, PBMC	7,6	2,3	5,4	1,4
JAIDS	ALENCAR 13	Varios	Varios	2009	300	BD	PLASMA	12	4,2	7	3
J Int AIDS Soc	de MORAES, CASEIRO 14	Varios	Varios	2010	329	HIVC	Papel Filtro	11,6			
J Int AIDS Soc	de MORAES, CASEIRO 14	Manaus	AM	2010	47		Papel Filtro	8,5			
J Int AIDS Soc	de MORAES, CASEIRO 14	Salvador	BA	2010	47		Papel Filtro	17			
J Int AIDS Soc	de MORAES, CASEIRO 14	Brasilia	BR	2010	47		Papel Filtro	10,6			
J Int AIDS Soc	de MORAES, CASEIRO 14	Rio de Janeiro	RJ	2010	47		Papel Filtro	12,8			
J Int AIDS Soc	de MORAES, CASEIRO 14	Porto Alegre	RS	2010	47		Papel Filtro	12,2			
J Int AIDS Soc	de MORAES, CASEIRO 14	Santos	SP	2010	47		Papel Filtro	17			
J Int AIDS Soc	de MORAES, CASEIRO 14	Itajaí	SC	2010	47		Papel Filtro	4,4			

Resistência no Brasil

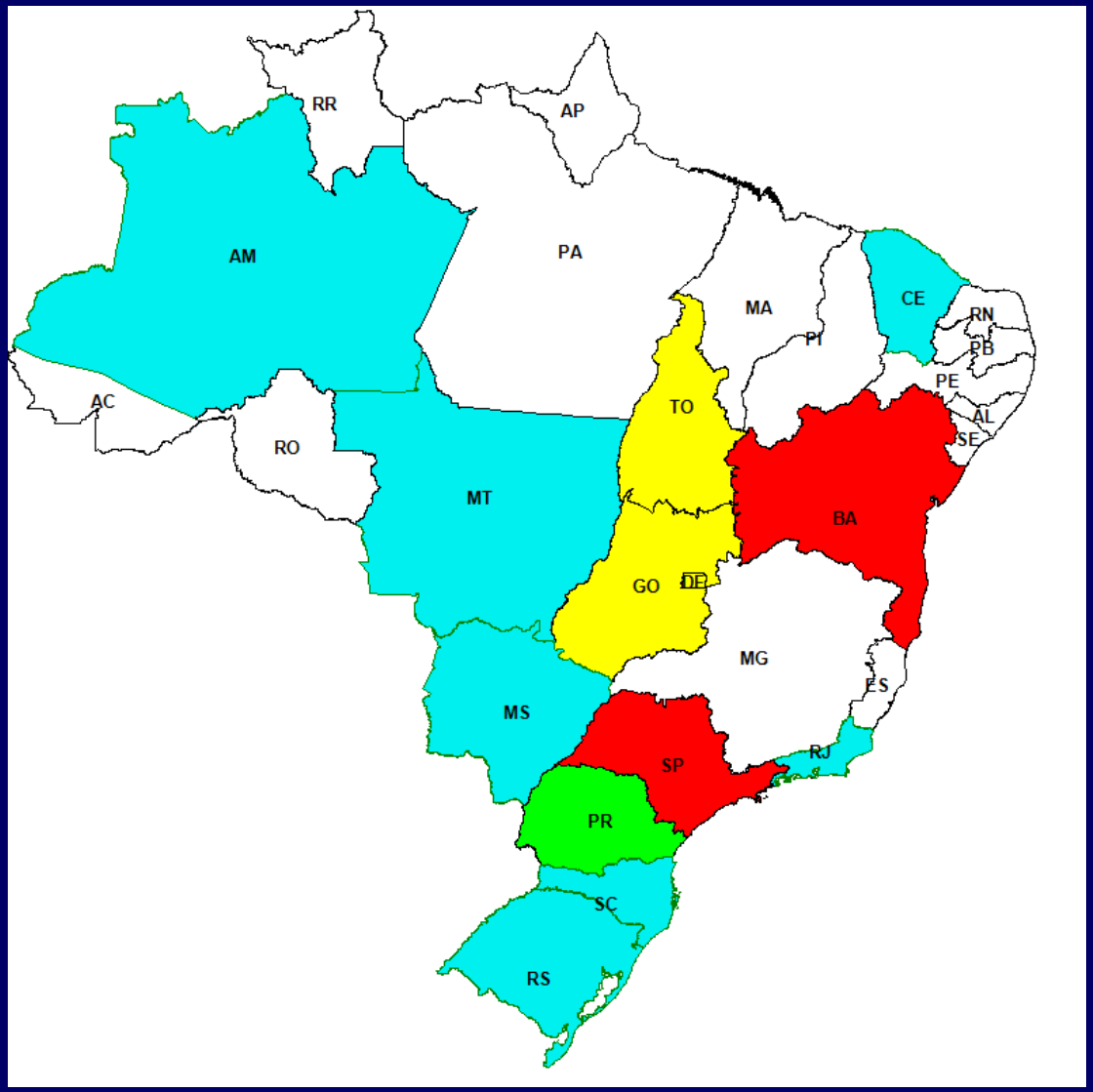


Legenda

BR_Estados por RES_TOTAL

- 20 para 33,7 (1)
- 15 para 20 (1)
- 10 para 15 (2)
- 5 para 10 (5)
- 0 para 5 (18)

Resistência no Brasil

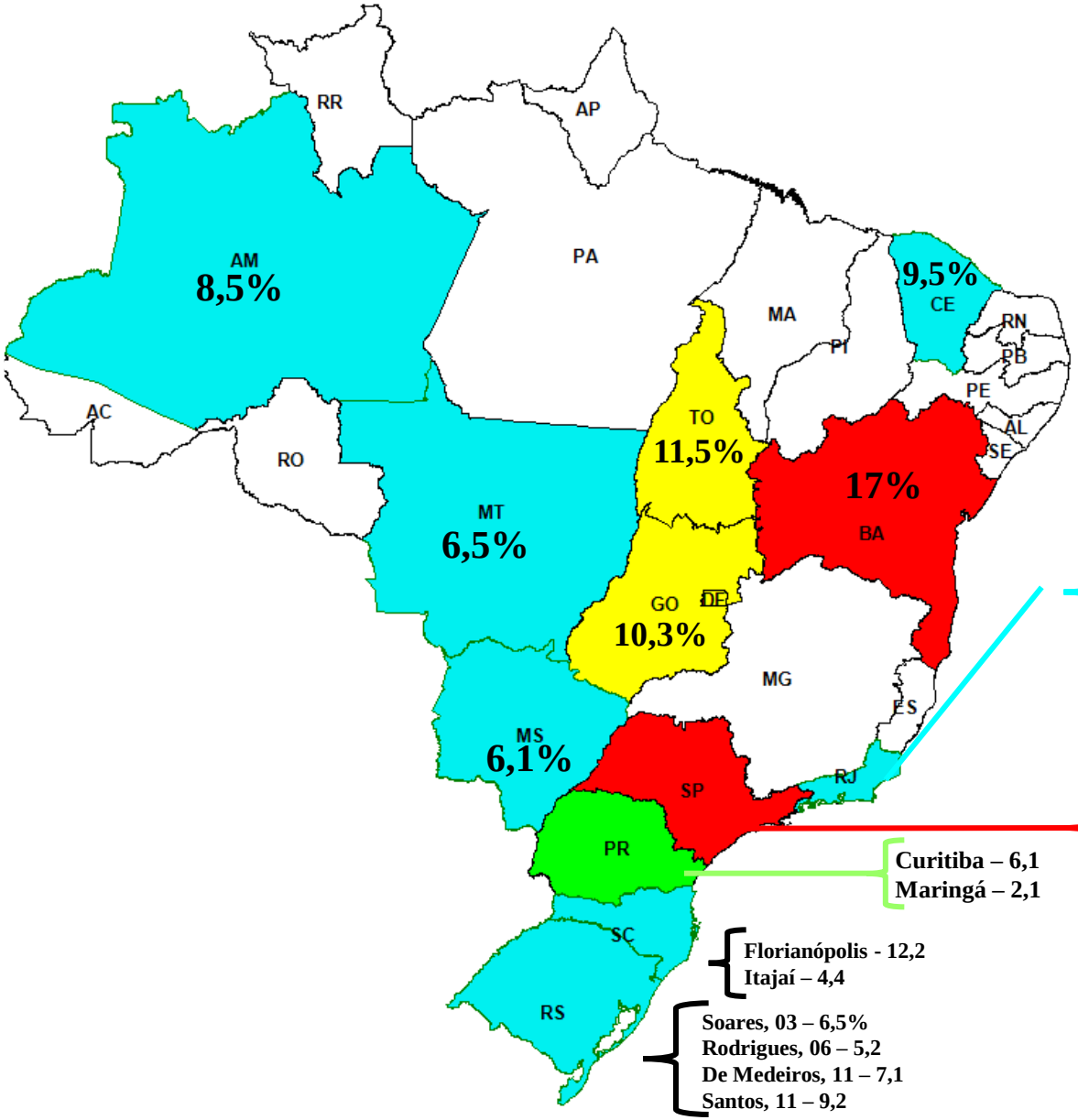


Legenda

BR_Estados por MÉDIA

- 15 para 20 (2)
- 10 para 15 (3)
- 5 para 10 (7)
- 1 para 5 (1)
- 0 para 0 (14)

Resistência no Brasil



Dumans, 98 – 8,5%
Varella, 00 – 0%
Maia Teixeira, 00 – 15,4%
Pires, 02 – 10,2%
Moraes, 10 – 12,8%

Santos, 99 – 22,7%
Santos, 02 – 33,7%
Santos, 07 - 23,3%
Santos, 10 - 17%
São Paulo – 04 – 10%
São Paulo – 05 – 2,9%
São Paulo – 06 – 9,7%
São Paulo – 09 – 7,6%

Curitiba – 6,1
Maringá – 2,1

Florianópolis - 12,2
Itajaí – 4,4

Soares, 03 – 6,5%
Rodrigues, 06 – 5,2
De Medeiros, 11 – 7,1
Santos, 11 – 9,2

Resistência no Brasil

de Moraes Soares CMP et al. *Journal of the International AIDS Society* 2014, **17**:19042
http://www.jiasociety.org/index.php/jias/article/view/19042 | http://dx.doi.org/10.7448/IAS.17.1.19042

JIAS Journal of the International AIDS Society

Research article

Prevalence of transmitted HIV-1 antiretroviral resistance among patients initiating antiretroviral therapy in Brazil: a surveillance study using dried blood spots

City/region	Mean age (variation)	Males (%)	Mean CD4	Mean VL $\log_{10}$	TDR (%)	2 classes resistance (%)	3 classes resistance (%)
Manaus/N	36 (18–61)	59.6	320 (91–781)	4.6 (2.4– >5.7)	8.5	2.1	
Salvador/NE	38 (19–58)	60.9	227 (3–581)	5.2 (3.7–5.9)	17.0	4.3	
Brasilia/MW	40 (21–63)	77.1	235 (24–644)	5.3 (2.0–6.3)	10.6	4.3	
Rio de Janeiro/SE	41 (27–76)	89.4	233 (25–447)	5.2 (3.5–5.9)	12.8	4.3	
Porto Alegre/S	41 (18–65)	63.3	249 (35–759)	5.1 (3.0– >5.7)	12.2	2.0	
Santos/SE	40 (26–69)	65.7	285 (11–861)	4.9 (2.7–5.5)	17.0	3.7	1.9
Itajaí/S	39 (25–63)	65.9	247 (15–475)	5.2 (2.4–6.2)	4.4	2.2	
Total	39 (18–76)	69.0	253 (3–861)	5.2 (2.0–6.3)	11.6	3.3	0.3

Forty-seven samples have been collected for each site.

Resistência no Brasil

de Moraes Soares CMP et al. *Journal of the International AIDS Society* 2014, **17**:19042
http://www.jiasociety.org/index.php/jias/article/view/19042 | http://dx.doi.org/10.7448/IAS.17.1.19042

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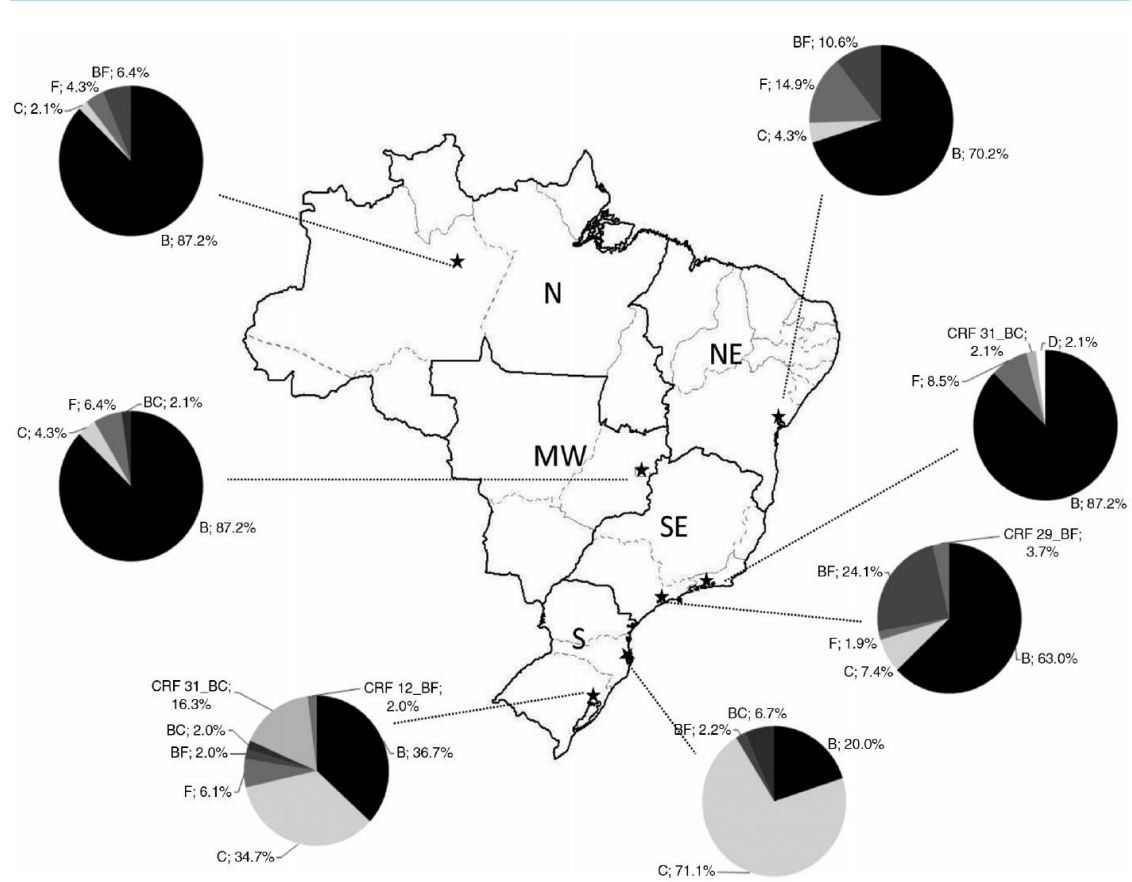

Devemos Genotipar antes de tratar ?

HIV/AIDS MAJOR ARTICLE

Should Resistance Testing Be Performed for Treatment-Naive HIV-Infected Patients? A Cost-Effectiveness Analysis

Paul E. Sax,[1] Runa Islam,[2] Rochelle P. Walensky,[1,2,3] Elena Losina,[2,5] Milton C. Weinstein,[4] Sue J. Goldie,[4] Sara N. Sadownik,[2] and Kenneth A. Freedberg[2,3,4,5]

[1]Division of Infectious Diseases, Brigham and Women's Hospital, Divisions of [2]General Medicine and [3]Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, [4]Harvard Center for Risk Analysis, Harvard School of Public Health, and [5]Departments of Biostatistics and Epidemiology, Boston University School of Public Health, Boston, Massachusetts

Clinical Infectious Diseases 2005; 41:1316–23
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Devemos Genotipar antes de tratar ?

Prevalence of primary resistance in population, %	Test cost of $400		Cost-effectiveness by test cost, $/QALY		
	Incremental cost, $	Life expectancy gained, QALMs	$400	$200	$800
0.25	430	0.03	175,400	97,200	331,500
0.5	480	0.06	97,300	58,200	175,400
1.0	580	0.1	58,300	38,700	97,300
1.5	670	0.2	45,200	32,200	71,300
3.0	950	0.4	32,200	25,700	45,200
5.0	1300	0.6	27,000	23,100	34,800
7.0	1700	0.8	24,800	22,000	30,400
8.3[a]	2000[a]	1.0[a]	23,900[a]	21,600[a]	28,600[a]
9.0	2100	1.1	23,600	21,400	27,900
10.0	2300	1.2	23,100	21,200	27,000

Clinical Infectious Diseases 2005; 41:1316–23
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Devemos Genotipar antes de tratar ?

Conclusions. Genotype-resistance testing of chronically HIV-infected, antiretroviral-naive patients is likely to improve clinical outcomes and is cost-effective, compared with other HIV care in the United States. Resistance testing at the time of diagnosis should be the standard of care.

Teste de resistência no momento do diagnóstico deve ser o padrão no atendimento

Clinical Infectious Diseases 2005; 41:1316–23
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O que dizem os consensos?

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

access AIDS*info* mobile site

DHHS

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug-resistance testing is recommended regardless of whether antiretroviral therapy (ART) is initiated immediately or deferred **(AII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is initiated immediately, drug-resistance testing can determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained after treatment initiation. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay generally is preferred **(AIII)**.	If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least 1 drug is seen in 6% to 16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered before initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing before initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If an INSTI is considered for an ART-naive patient and transmitted INSTI resistance is a concern, providers may supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays)	(see Co-receptor Tropism Assays)

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 27, Number 3, 2011
© Mary Ann Liebert, Inc.
DOI: 10.1089/aid.2010.0150

CLINICAL PERSPECTIVE

The Association Between Primary Antiretroviral Resistance and HAART Virologic Failure in a Developing Set

Luiz Henrique Gagliani,[1,2] Wagner T. Alkmim Maia,[1] Dercy Sá-Filho,[2] Luiz Mario Janini,[1]
Maria Cecilia Sucupira,[1] Marcos Montani Caseiro,[2] and Ricardo Sobhie Diaz[1]

MATERIAL E MÉTODO

- **Grupo 1** (N=43) são os pacientes que após a introdução do tratamento aos antiretrovirais **não conseguiram** atingir os níveis de quantificação de carga viral abaixo de 50 cópias/ml, isto é a carga viral se manteve detectável após seis meses de tratamento.

- **Grupo 2** (N=37) são os pacientes **conseguiram** se manter com os níveis de quantificação da carga viral, indetectáveis após seis meses de tratamento.

Após 6 , 12 meses e 10 anos

	Grupo 1	Grupo 2	Resistência G1+G2
Número de Pacientes	43	37	

Obrigado

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