

Renic Studies Brazil

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Survey of HIV primary resistance needs a standardized mutation list

- Shafer et al, *Aids* (2007) proposed a list where:
 - IP: 31 mutations in 14 positions .
 - NRTI: 31 mutations in 15 positions+ T215 revertants
 - NNRTI: 18 mutations in 10 positions.

Robert W. Shafer^a, Soo-Yon Rhee^a, *AIDS* 2007, 21:215–223

How to count HIV primary
resistance ?

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update

Position	AA	Lists	New	A (%)	AE (%)	AG (%)	B (%)	C (%)	D (%)	F (%)	G (%)	No Rx (Max %)	Max Rx (%)
<i>Number of individuals:</i>				1,305	770	1,035	5,672	2,020	324	265	403	11,784	14,621
100	I	5		0	0	0	0	0	0	0	0	0	5.4
101	E	5		0	0	0	0.2	0	0	0	0	0.2	6.4
	P	5	✓	0	0	0	0	0	0	0	0	0	1.4
103	N	5		0.1	0	0.2	0.3	0.2	0	0	0	0.3	40
	S	4		0	0	0	0	0	0	0	0	0	0.6
106	M	5		0	0	0	0	0	0	0	0	0	12
	A	5		0	0	0.1	0	0	0	0	0	0.1	1.1
179	F	5	✓	0	0	0	0	0	0	0	0	0	0.2
181	C	5		0.1	0.1	0.1	0	0.1	0	0	0	0.1	14
	I	5		0.1	0	0	0	0	0	0	0	0.1	1.1
	V	5	✓	0	0	0	0	0	0	0	0	0	1.1
188	L	5		0	0.3	0	0	0	0	0	0	0.3	2.4
	H	5		0	0	0	0.1	0	0.3	0	0	0.3	0.6
	C	5		0	0	0.1	0	0	0	0	0	0.1	0.9
190	A	5		0.1	0	0	0	0.1	0.3	0	0	0.3	10
	S	5		0	0	0	0	0	0	0	0	0	1.6
	E	4		0	0	0.1	0	0	0	0	0	0.1	0.5
225	H	5		0	0	0	0	0	0	0	0	0	7.6
230	L	3		0	0	0	0	0	0	0	0	0	3.6
<i>Sum of Prevalences:</i>				0.4	0.4	0.6	0.7	0.5	0.6	0	0		

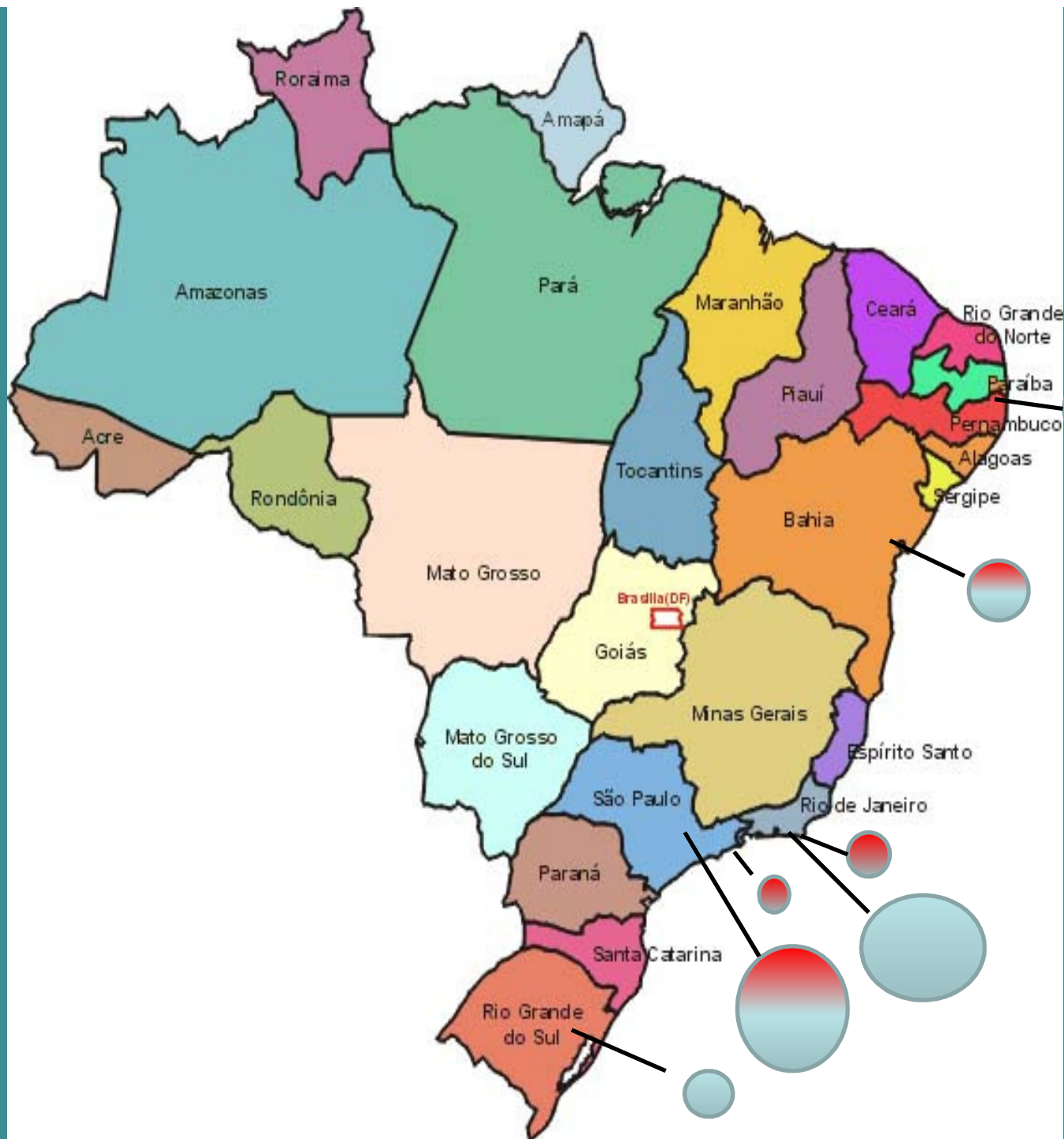
Abbreviations: Pos – amino acid position; AA – amino acid difference from consensus B; Lists – Number of mutation lists with the mutation; New – mutations not present on the 2007 SDRM list; No Rx – highest prevalence in untreated persons in any of the 8 listed subtypes; Max Rx – Prevalence of the mutation in the subtype with the highest prevalence of the mutation provided the mutation is present in viruses from two or more individuals.

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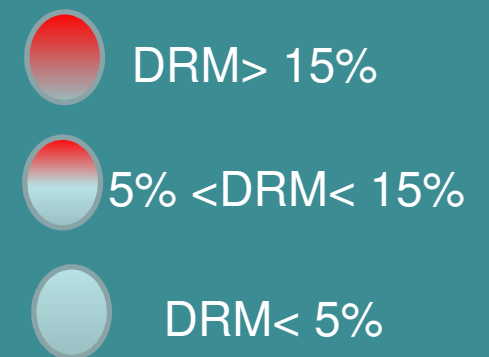
HIV DR Mutations impacting in RC (*viral fitness*)



***Mutations 41 + 67 + 70 + 215 + 219**



Primary Resistance in Brazil 2008-2013



RENIC Study

- What is RENIC?

Rede Nacional de Identificação e
Caracterização do HIV.

BRESNET

Brazilian Resistance Network

Brazilian Network for HIV Drug Resistance Surveillance (HIV-BResNet): a survey of chronically infected individuals

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Mariza G. Morgado^d, Ivone L. Pires^{e,f}, Luís Brigido^g, Maria C. Dantas^h,
Draurio Barreira^h, Paulo R. Teixeira^h, Amílcar Tanuri^a and the Brazilian
Network for Drug Resistance Surveillance**

AIDS 2003, 17:1063–1069

Keywords: drug resistance, genotyping, HIV surveillance

- RENIC/BRESNET Started in 2001 to study the HIV primary resistance in Brazil.
- 1st survey was done in 2002 targeting recent diagnosed patients attending VCT sites spread in spanned metropolitan regions located in eight different Brazilian states, Rio Grande do Sul (n ¼ 139), Parana (n= 147), Sao Paulo (n = 100), Rio de Janeiro (n = 83), Mato Grosso do Sul (n = 7), Para (n ¼=17) , Bahia (n = 12), and Ceara (n =30), that covered 65% of Brazilian AIDS Epidemic.

RENIC2002 Characteristics

Table 1. Epidemiological data.

Characteristics	Number (%)
Gender: male	225 (59.2)
Age (years, mean $\pm$ SD)	30.7 $\pm$ 9.1
Risk factor for HIV ^a	
Homosexual	55 (19.71)
Heterosexual	172 (61.65)
Intravenous drug user	14 (5.02)
Bisexual	20 (7.17)
Other/multiple	18 (6.45)
Partner	
HIV positive ^b	145 (39.61)
HIV positive and using antiretroviral therapy ^c	44 (30.34)

^aCalculation based on 279 individuals who respond to this item of the questionnaire. ^bCalculation based on 366 individuals who respond to this item of the questionnaire. ^cCalculation based on 145 individuals who respond to this item of the questionnaire.

RENIC2002 Primary DRM

Table 2. Genotypic distribution of primary mutations found.

Site	Epidemiological data			NRTI	NNRTI	PI
	Sex	Age (years)	Risk factors			
Rio de Janeiro						
RJ877	F	38	het; parHIV; parARV		V106I	
RJ925	M	29	hom; parHIV; parARV		V106I	
RJ897	M	22	het			G48V,I54T,V82A
RJ866	F	36	het		K103N	
RJ928	F	36	het; parIDU			V32I,M46I,I47V,V82A
Rio Grande do Sul						
RS2032	F	47	het; parHIV	M41L;D67N;T215F		
RS2093	F	39	het			I54V,L90M
RS2071	F	22	het; parHIV	M41L; M184V		
RS2152	M	37	het; parHIV			M46I,I54V,V82A
RS2017	M	37	bisex; parHIV			G48V;I54T;V82A
RS2161	F	37	het; parIDU			I84V
Paraná						
PR1483	M	28	hom		V106I,V108I	
PR1518	M	17	het; parHIV	M41L		
PR1537	F	37	het	M184V		
PR1538	M	24	hom	M41L		
São Paulo						
SP469	M	48	bisex; parHIV		V108I	
SP653	M	54	het	M41L	V108I	
SP369	M	37	het			D30N
Centre North (Pará + Mato Grosso do Sul)						
CN28	M	39	het; parHIV	M41L		
CN2398	F	35	mult		V106I	
Northeast (Ceará + Bahia)						
NE269	F	38	het; parHIV			V82S
NE135	M	26	bisex	M41L		
Genomes with primary mutations				8 (2.31% ^a)	7 (2.06% ^a)	8 (2.31% ^b)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; F, female; M, male; hom, homosexual; het, heterosexual; bisex, bisexual; mult, multiple risk factors; parHIV, sexual partner HIV positive; parIDU, partner intravenous drug user; parARV, partner taking antiretroviral therapy. ^aPercentage based on 339 reverse transcriptases sequenced. ^bPercentage based on 356 proteases sequenced.

RENIC2007/8 Characteristics

- A new RENIC survey was placed in 2007/8. This done using the HIV Threshold Survey methodology (HIV-THS, WHO), targeting the four major Brazilian regions, selecting the 6 more populated state capitals, Sao Paulo, Rio de Janeiro, Salvador, Porto Alegre, Brasilia, and Belem.
- We were able to sequence samples from 210 individuals with recent HIV diagnosis, 17 of them (8.1%) carrying HIV isolates with primary antiretroviral resistance mutations. Five, nine, and four isolates showed mutations related to resistance to NRTIs, NNRTIs, and PIs, respectively. Using HIV-THS we could find an intermediate level of resistance (5%-15%) in Belem/Brasilia, Sao Paulo and Rio de Janeiro, whereas lower level of resistance (<5%) was observed in the other areas.

RENIC2007/8 Characteristics

Epidemiological Data	
Characteristics	Number (%)
Gener (male)	45
Age (years)	36 $\pm$ 8

Risk factor HIV (%)	
Homosexual	23.6
Bisexual	11
Heterosexual	56.1
Intravenous drug user	0
Blood transfusion	1.6
Other / multiple	8.7

RENIC2007/8 Characteristics

Biological Parameters

CD4 (Cells/mm ³ ,) ^a	575 ± 221
Viral load (Log of copies/ml) ^b	4.58 ± 4.75

^a and ^b – Calculation based on 187 and 156 individuals who respond to this item on the questionnaire, respectively.

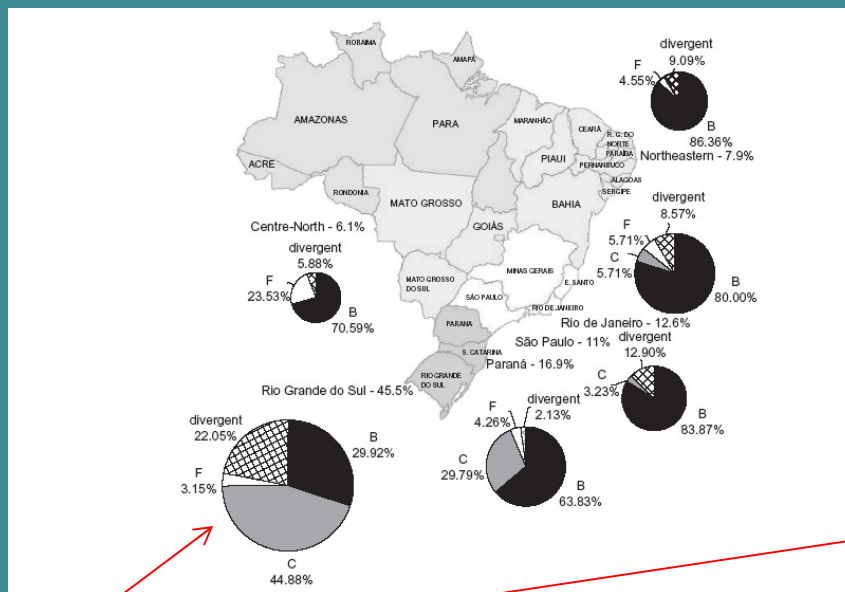
Table 2: Genotypic distribution of primary mutations and level of resistance per site

Site	Number of primary mutation found			Level of Resistance ¹
	NRTI	NNRTI	PI	
Sao Paulo (n = 3)				5%-15%
SP015		K103N	M46I	
SP022		K103N, K238T		
SP041		K103N		
Rio de Janeiro (n = 7)				5%-15%
RJ406		K103N		
RJ529			L90M	
RJ565	T69D			
RJ578	T215E, K219R			
RJ026			M46I	
RJ064	M41L, T215C/S			
RJ067			M46I	
Brasilia/Belem (n = 3)				5%-15%
BE010		K103N		
DF 058	M184V/M			
Salvador (n = 1)				< 5%
SA023		K103N		
Porto Alegre (n = 1)				< 5%
PA020			V82A	

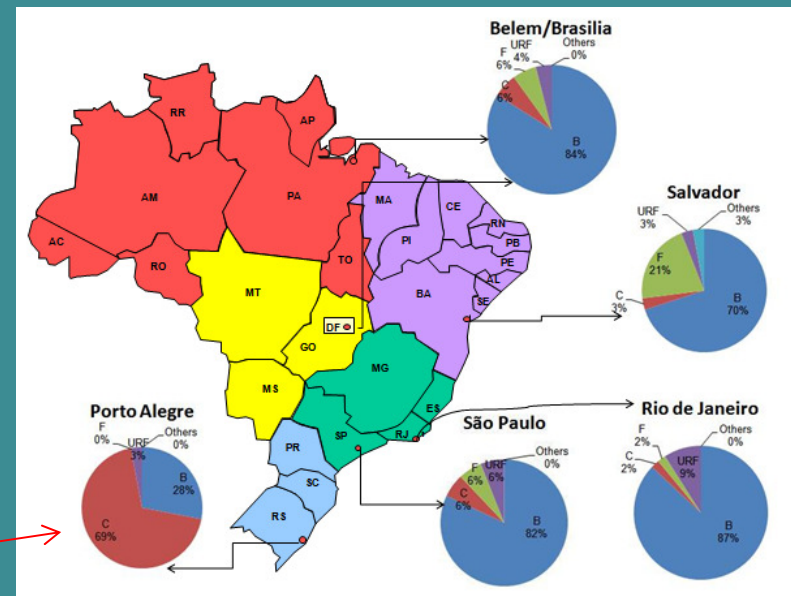
17 /210 (8.1%)

HIV-1 subtype prevalence in Brazil

RENIC2002

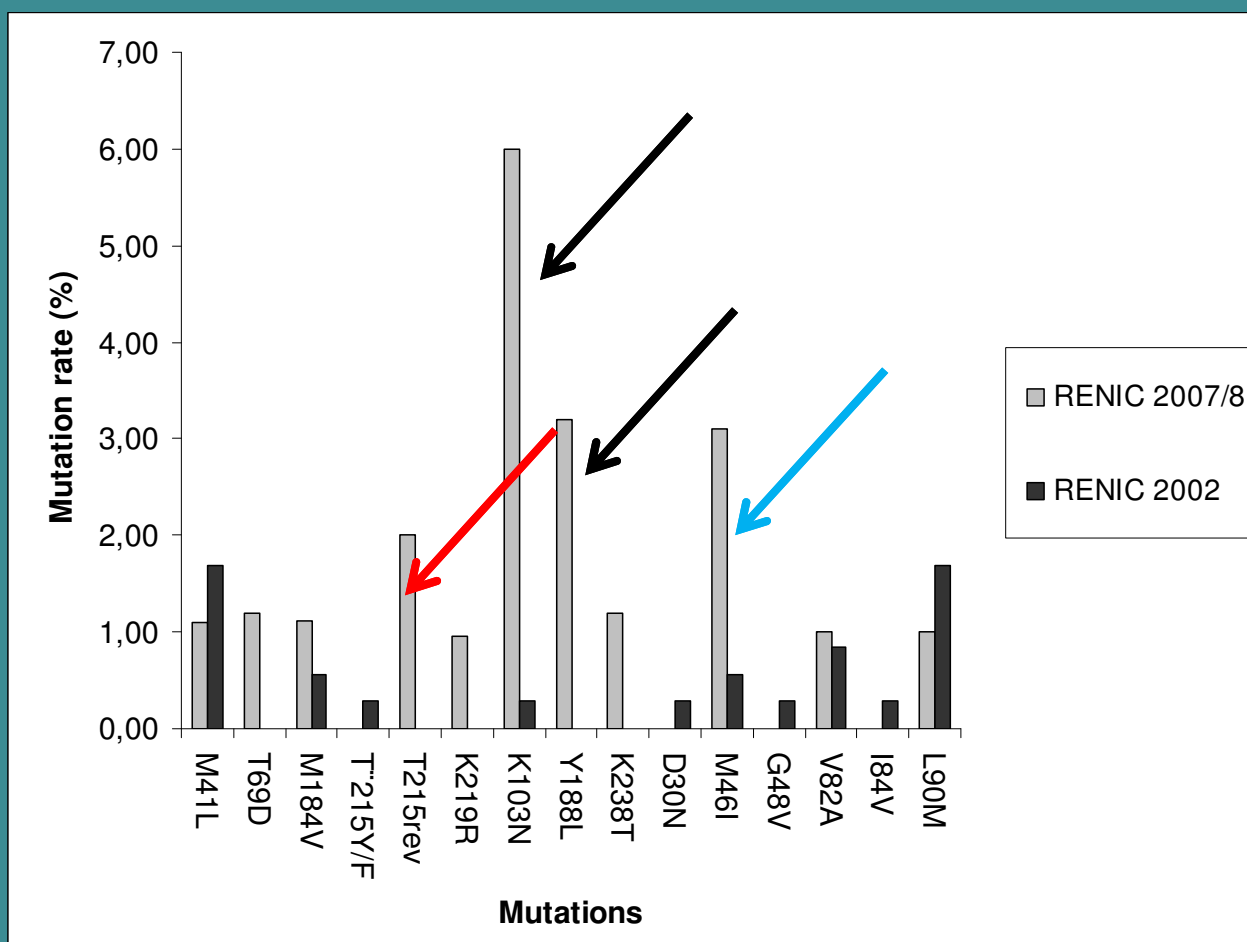


RENIC2007/8



New subtypes found in Brazil: CRF2-AG, and A.

Primary resistance trend in Brazil Comparing RENIC 02 X 07/8



RENIC 2013

- RENIC 2013 will target individuals recently diagnosed going to CD4 labs to get 1st CD4 enumerations for clinical staging.
- In 2010 we had 42000 individuals in this condition in our CD4 lab network .

We calculated a minimum sample size per stratum considering the prevalence of resistance parameter of 5.4% (Ferreira et al., 2011), bilateral error of 2% and a confidence interval of 95%. For each of the 10 strata, we applied the correction factor for finite populations in the minimum sample size, considering the number of treatment-naïve patients who had their first exam for CD4 cell count in 2011. It was, also, a loss of 10% and design effect (Deff) of 1.25.



Stratum	minimal #	corected	Lost + DEFF (1.25)	n final
North	491	442	601	610
PE	491	424	574	600
BA	491	401	540	550
Restante do NE	491	447	608	610
SP	491	470	643	700
RJ	491	451	615	650
MG+ES	491	434	589	600
RS	491	450	613	650
SC+PR	491	444	605	600
CO	491	420	569	600
Total	4906	4383	5957	6170

- In a second stage sampling we divided the number of samples per stratum by the CD4 lab in each one relating to the number of individuals in the inclusion criteria .

Second stage sampling (CD4 Labs)

	Laboratório Executor	n
atum 1 North		
RO	Laboratório Central de Saúde Pública de Rondônia	65
AC	Laboratório Central de Saúde Pública do Acre	16
AM	Fundação de Medicina Tropical do Amazonas	200
RR	Laboratório Central de Saúde Pública de Roraima	24
PA	Laboratório Central de Saúde Pública do Pará	220
PA	Laboratório de Virologia - Universidade Federal do Pará	29
AP	Laboratório Central de Saúde Pública do Amapá	22
TO	Laboratório Central de Saúde Pública de Tocantins	34
atum 2 Northeast		
MA	Laboratório Central de Saúde Pública do Maranhão	118
MA	Laboratório de Imperatriz do Maranhão	23
PI	Laboratório Central de Saúde Pública do Piauí - Dr. Costa Alvarenga	68
CE	Laboratório Central de Saúde Pública de Juazeiro do Norte	11
CE	Laboratório Central de Saúde Pública do Ceará	106
CE	Laboratório Central do Município de Fortaleza	43
RN	Laboratório Central de Saúde Pública do Rio Grande do Norte	67
PB	Laboratório Central de Saúde Pública da Paraíba	72
AL	Laboratório Central de Saúde Pública de Alagoas	60
SE	Instituto Parreiras Horta - Lacen SE	42
atum 3 Pernambuco		
PE	Laboratório Central de Saúde Pública de Pernambuco	481
PE	Laboratório Municipal do Recife	119

Próximos passos da RENIC 2009

- Mudar o nome para RENIC 2010 e organizar um Cronograma Realista do Estudo
- Acabar o protocolo e submeter a CONEP.
- Definir os PTVs para o estudo e contatá-los para verificar disponibilidade para o estudo.
- Organizar uma reunião com os PI dos PTVs e dos labs em Brasília para apresentação do estudo e assinatura de termo de compromisso.
- Data de inicio do RENIC2010