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Surveillance of HIV drug resistance mutations in HIV patients from Panama receiving ARV drugs during the last two years

J. A. Castillo[1], G. Arteaga[1], C. González[1], Y. Mendoza[1], A. A. Martínez[1], R. Samaniego[2], D. Estripeaut[3], N. Sosa[1], J. M. Pascale[1].

(1)Gorgas Memorial Institute for Health Studies, (2)Hospital Santo Tomás, (3)Hospital del Niño, Republic of Panama.

Abstract

With the aim of improving the quality of life of subjects living with HIV, Panamanian health authorities offered free anti-retroviral (ARV) drugs since 1999. The National HIV Program initiated in 2001 antiretroviral drug treatment (ARVT) to all infected individuals needing medication according to the international guidelines. Initially, nucleoside (NRTI) and non nucleoside (NNRTI) inhibitors of reverse transcriptase were used, followed by protease inhibitors (PI) in 2005. The 2007 National Guidelines for the Treatment of HIV infected subjects established the use of four different groups of ARV drugs[1](Table1). During 2010 and 2011, two new groups of drugs: integrase inhibitors and CCR5 antagonist were also freely available[2]. It is well known that mutations generated inside the HIV genome reduces the efficacy of antiretroviral therapy representing the main reason for therapy failures. The development of new drugs and the design of new treatment schemes leaded us to follow monitoring and implementing surveillance programs to generate data to support the use or change of specific ARV drugs in our country.

Materials & Methods

A total of 184 samples from treated HIV patients, with suspect of therapeutic failure, were collected from February 2010 to January 2012. Viral RNA was extracted and HIV *pol* region (Figure 1) was reverse-transcribed, amplified (1.2Kb) and sequenced following Viroseq™ manufacturer procedure and/or an in-house method previously described[3]. The sequences were used to genotype and analyze reverse transcriptase and protease genes for specific mutations associated with drug resistance in HIV-1. The genotypic drug resistance interpretation was performed using the Stanford algorithm. Mutation data was analyzed based on International AIDS Society (IAS) table of mutations[5].

Table 1. ARV treatment in Panama according the population to be treated.

POPULATION	TREATMENT GUIDELINES IN PANAMA	
	2007	2011
Adults	2 NRTI +1 NNRTI 1. AZT +3TC +EFV (preferred option) 2. FTC + TDF +EFV	2 NRTI +1 NNRTI 1. 3TC or FTC + TDF +EFV (preferred option) 2. AZT + 3TC +EFV
Pregnancy woman	2NRTI + 2IP 1. AZT + 3TC (Combivir®) + Lopinavir + Ritonavir (Kaletra®) 2. AZT + 3TC (Combivir®) + Saquinavir + Ritonavir	2NRTI + IP/r or NVP 1. AZT + 3TC (Combivir®) + Lopinavir + Ritonavir (Kaletra®) 2. AZT + 3TC (Combivir®) + Saquinavir + Ritonavir
Newborn*	AZT AZT + 3TC or FTC + NVP	AZT AZT + 3TC or FTC + NVP
Child < 3 years old	2NRTI + LPV/r AZT + 3TC + LPV/r	2NRTI + LPV/r 1. AZT + 3TC or FTC + LPV/r 2. AZT + 3TC or FTC + NVP
Child > 3 years old	2NRTI + EFV AZT + 3TC + EFV	2NRTI + 1NNRTI 1. AZT + 3TC + EFV 2. AZT + 3TC + LPV/r

***Depends on the mother treatment regimen during the pregnancy.**

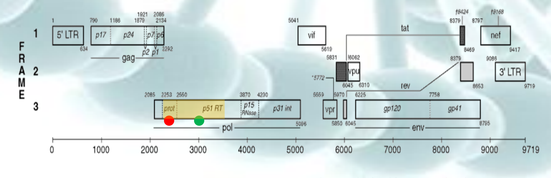

Image obtained from: www.losalamos.com

Figure 1. HIV genomic map showing the *pol* gene region sequenced by Viroseq™ and in-house genotyping method. Protease gene (red dot) sequenced consist of 99 amino acids and reverse transcriptase gene (green dot) arround 330 amino acids.

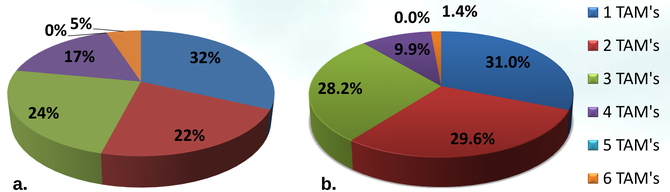

Figure 2 Thymidine-associated mutations. (a) Accumulative percentage of TAM's mutations from 2007-2010. Data kindly provided by *G. Arteaga et al.*[4] (b) Accumulative percentage of TAM's mutations from 2010-2012.

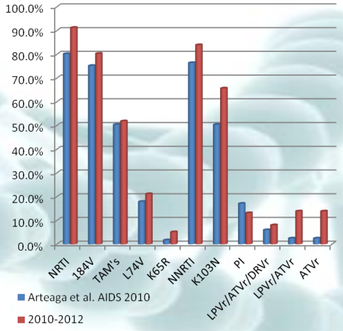

Figure 3. Comparison between mutations reported in 2010 and 2010-2012.

Table 2. Comparison of mutations reported between period prior and after 2010

ARV	Arteaga et al. AIDS 2010 n=117		2010-2012 n=137	
	Number	Percentage	Number	Percentage
NRTI	**94**	**80.2%**	**125**	**91.2%**
184V	88	75.2%	110	**80.3%**
TAM's	59	50.4%	71	**51.8%**
L74V	20	17.9%	29	**21.2%**
K65R	1	1.7%	7	**5.1%**
NNRTI	**89**	**76.4%**	**115**	**83.9%**
K103N	59	50.4%	90	**65.7%**
PI	**20**	**17.1%**	**18**	**13.1%**
LPVr/ATVr/DRVr	7	6.0%	11	**8.0%**
LPVr/ATVr	4	2.5%	19	**13.9%**
ATVr	4	2.5%	19	**13.9%**

Results

We found 137 of 162 (84.6%) samples with at least one clinical significant mutation related to the ARV's used in Panama associated to RT and protease genes. We detected 125 (91.2%) of these samples with mutations that affected nRTI drugs and 115 samples (83.9%) showed variations affecting NNRTI effectiveness.(Table 2) M184V and K103N mutations were present in 80.3% (110/137) and 65.7% (90/137) of the samples, respectively.(Figure 2,3) We detected 18 samples (13.1%) with mutations associated to resistance to protease inhibitors.

Conclusion

Panama has improved the coverage of medication and the service of surveillance of HIV drug resistance mutations during the last two years by the use of new and better technologies that allowed us to evaluate a greater number of patients. The prevalence of clinical significant mutations in patients with suspect of therapeutic failure, related to one or more ARV drugs used to treat HIV patients was 84.6% in this analysis showing a percentage increase of 13.3% of the presence of mutations compared to previous data, this increment is associated to nRTI's and NNRTI's drugs. Mutations in protease gene were observed in 13.1% of the specimens with mutations to any inhibitor.

References

1. Ministerio de Salud Panamá y Organización Panamericana de la Salud. Normas para el manejo terapéutico de las personas con VIH en la República de Panamá. Panama City: Ministry of Health; 2007.
2. Ministerio de Salud Panamá y Organización Panamericana de la Salud. Normas para el manejo terapéutico de las personas con VIH en la República de Panamá. Panama City: Ministry of Health; 2011.
3. Castillo J, Arteaga G, Mendoza Y, Pascale JM, et al. HIV transmitted drug resistance in adult and pediatric populations in Panama. Rev Panam Salud Publica. 2011 Dec;30(6):649-56.
4. Arteaga G, Castillo J, Martínez A, Mendoza Y, et al. Prevalence of HIV drug resistance in treatment experienced, chronically HIV-infected individuals from Panama conference presentation]. At: XVIII International AIDS Conference, Vienna, 18–23 July 2010
5. Victoria A. Johnson, et al. Update of the drug re-sistance mutations in HIV: November 2011- International AIDS Society. Topics in HIV Medicine 19: 156-164.

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